UNITED STATES

Armed Forces Medical Journal

VOL. 11 • NO. 11 • NOVEMBER 1960

Published Monthly
by the Armed Forces Medical Publication Agency
Department of Defense

Editor, pro tem
BENNETT F. AVERY
Captain, Medical Corps
United States Navy

Associate Editor
MAY SHERMAN, M.D.

Editorial Board
JOHN B. COATES, JR., Colonel, MC, USA
DONALD R. CHILDS, Captain, MC, USN
JOHN F. DOMINICK, Colonel, USAF, MC

Monthly Message

Military medicine in time of war. Here care of patients is only a part, important though it may be. Military medicine now becomes a necessity for the Regular Officers in the three services: to know how to plan with and advise the high commands as to numbers of casualties; provision for their care; preventive medicine and sanitation; supply under all sorts of conditions during offense and defense; evacuation systems—air, sea, ground, rail or mule; training of the Reserve and Civilian Components; flexibility in personnel assignments or temporary attachments; economical use of equipment; positioning of hospitals temporary or permanent; sufficient knowledge of the military so as to utilize medical capabilities to the greatest potential at all times; and here in the States a regulating system, so well established during the days of World War I and expanded in World War II, must be understood and coordinated to function smoothly and provide prompt and orderly disposition of patients. We have no idea of the type of war which may be forced upon and may confront us. Will it be like past experiences or will it consist of massive attacks on the United States with widespread destruction and mass casualties in many areas simultaneously? Unless we have flexibility in planning and the realization of all possibilities there will be confusion. For example, at the onset of World War II, at a meeting in April 1942 in New York, I suggested the possibility of air evacuation, successfully demonstrated by the Germans. My panelists, one a distinguished civilian surgeon and the other a prominent surgeon in Service, said it was impractical, dangerous, and that planes could not fly at a greater altitude than 1,500 feet with safety for patients. We were keyed to the plush railroad evacuation system of France in World War I; yet in January 1943, nine months later, some of our units were in Eastern Algeria. There was a single-track railroad along the Coast back to Algiers and Oran, approximately 1,200 miles; immediately we adopted what only a few months before I had been told was impossible—air evacuation with success and comfort!

In Korea we discarded a combat hospital system which had been eminently successful in the rapid movement in the Italian and European Theatres in World War II. This change was not sound, yet worked well enough in that limited theatre. On the other hand, a common supply and distribution system was instituted for all three services, based upon the common procurement agency instituted in World War II for the Army and Navy.

Frank B. Berry

FRANK B. BERRY, M.D.,
Assistant Secretary of Defense
(Health and Medical)

Contents

U.S. ARMED FORCES MEDICAL JOURNAL • VOL. 11 • NOVEMBER 1960

Page

NOTICE TO READERS iv

MEDICAL SCIENCE

LEADERS ARE MADE—NOT BORN—*Robert B. Skinner* 1241

CLINICAL USE OF THE SECRETIN TEST—*James T. Hardy* . . . 1248

OUTBREAK OF UNIDENTIFIED DISEASE IN AMERICAN PERSONNEL IN ERITREA—*Jerome H. Greenberg, Perry W. Nadig* and *David L. Roberts* 1263

THE BATTLE OF BLOOD—*John G. Gibson, 2nd* 1276

COMPARISON OF CHLORAMPHENICOL, OXYTETRACYCLINE, AND PROCHLORPERAZINE IN SALMONELLA GASTROENTERITIS—*James E. Mc Guigan, Wilbur C. Berry* and *Philip R. Carlquist* 1288

POLYNEURITIS: CLINICAL REVIEW OF 23 CASES OF LANDRY-GUILLAIN-BARRÉ SYNDROME—*Roger C. Duvoisin* 1294

THE QUALITY OF MILITARY MEDICAL REPORTS—*Patsy M. Fiandaca, Jr.* 1307

SHIPBOARD TREATMENT OF VENEREAL DISEASES—*Reinhardt H. Bodenbender* 1311

OSTEOCHONDROSIS OF THE TARSAL SCAPHOID (KÖHLER'S DISEASE)—*Strother B. Marshall* 1319

BLOOD BANK ACCREDITATION—*John D. Voorhees* 1326

CLINICAL RESEARCH

STUDIES IN HUMAN ISOLATION I. PERCEPTUAL FINDINGS—*Sanford J. Freedman* and *Milton Greenblatt* 1330

USE OF A POROUS SYNTHETIC SPONGE (IVALON) IN SURGERY I. TISSUE RESPONSES AFTER IMPLANTATION—*Richard H. Adler* and *Clement Darby* 1349

ARMED FORCES INSTITUTE OF PATHOLOGY

CASE FOR DIAGNOSIS—*Samuel H. Rosen* 1365

CASE REPORTS

SPRENGEL'S DEFORMITY—*James D. Caskie* and *Robert D. Anderson* 1367

GONOCOCCIC ENDOCARDITIS—*Benjamin J. Gilson, Monroe E. Trout* and *Howard Alleman* 1375

MALIGNANT ISLET CELL ADENOMA OF PANCREAS WITH HYPOGLYCEMIA—*Ching-Chang Liu* and *Chu-Chiao Chang* 1379

OXYPHIL CELL TUMOR OF SUBMAXILLARY GLAND—*John B. Batsakis* and *Douglas G. Martz* 1383

URETHRAL FOREIGN BODY—*William E. Fraser* and *Allan Erde* . 1386

ARMED FORCES EPIDEMIOLOGICAL BOARD

ACTIVITIES OF THE COMMISSION ON INFLUENZA—*Fred M. Davenport* 1388

DEPARTMENTS

THIS IS YOUR A.M.A 1391

NEW BOOKS 1393

NOTICE TO READERS

The Editors regret to announce that the *United States Armed Forces Medical Journal* will cease publication with the December 1960 issue, completing volume 11.

As many as possible of the backlog of accepted articles will be published in the remaining issues. Manuscripts for which space cannot be found will be returned to the authors. No additional articles can be accepted.

Leaders Are Made—Not Born

BRIGADIER GENERAL ROBERT B. SKINNER, MC, USA

IN DISCUSSING MILITARY MEDICAL LEADERSHIP one soon realizes that the subject may be compressed into the general term "leadership." The word "military" can be eliminated because principles of good medical leadership apply equally to civilian medicine. Likewise, medical aspects of leadership are little different from leadership in all other phases of human endeavor.

During many years of association with military hospitals I have been interested in the qualities that lead to the success of hospital staffs, both individually and collectively. I have been particularly impressed with the distinctive atmosphere of each hospital that I have served.

Our Government, and the U.S. Army in particular, have spent considerable amounts of money to select and develop potential leaders. The Human Resources Office (HUMRO) set up by the Continental Army Command (CONARC) would like to develop guides for a military occupational specialty in leadership.

I am sure that the high position the Army medical service occupies in American medicine is directly attributable to the excellence of its military medical leaders, past and present. My association with its future medical leaders, at Brooke General Hospital and other places, makes me feel confident that the Army's dynamic leadership in American medicine will continue on its present high plane. However, in order to do this, it will be necessary to develop leadership potentialities to the fullest.

The pleasing bedside manner, the patient's confidence in the physician, interpersonal relationships throughout the hospital, keen interest and originality in research, and a burning desire for perfection in the practice of medicine are all outward manifestations of medical leadership.

I cannot recommend a better formula for command leadership

From Brooke General Hospital, Fort Sam Houston, Texas. Presented 8 March 1960, at a conference on military medicine at Brooke General Hospital.

than that given by Lieutenant General Leonard D. Heaton, MC, USA, surgeon general of the Army, quoting Dr. Karl T. Compton of the Massachusetts Institute of Technology: "I believe that experience, logic and human psychology all support the view that the type of government (command) most likely to be successful in the long run is the one that directs and inspires but does not too rigidly control; which offers large opportunity for initiative and criticism; which has faith in the mass judgment of an intelligent group and in the genius which may appear in unexpected quarters." I am sure General Heaton desired that this philosophy apply to all echelons of command in the Army Medical Service—hospital commander, chief of service, ward officer, or to anyone placed in a supervisory position over another individual.

I could stop at this point and say that everything in this discussion can be summarized in the Golden Rule: "Do unto others as you would have them do unto you." Nevertheless, it might be helpful to review briefly some of the fundamentals, the knowledge and the application of which, I feel, will lead to effective and dedicated leadership.

To many, in the past, the term "leadership" has suggested military leadership: General Pickett leading his brigade across the wheat field at Gettysburg; General Patton in a tank leading his Third Army; General Eichelberger on foot leading small units in the jungle fighting around Buna and Gona in New Guinea. Although these are outstanding examples of leadership, the same qualities that made these men leaders also apply to leadership in medicine, industry, religion, and politics; in fact, in every phase of human undertaking. Walter Reed, William Beaumont, Sir William Osler, and a host of other physicians in and out of the military services were just as truly leaders as were Washington, Lee, Lincoln, and Grant. Leadership is an abstract thing, and is difficult to define; yet no one has difficulty in recognizing good morale or good leadership when it is encountered in an organization.

"Leaders are born—not made" is an expression that has become hackneyed by use. Were it entirely true, this discussion would be futile. Like many maxims, however, it has only sufficient truth to merit its consideration. Undoubtedly, some leaders are born with natural endowments that help to sway others and cause them to follow with enthusiasm and loyalty. A commanding figure, an arresting voice, personality, and natural eloquence are attributes that are either impossible or very difficult for most to acquire.

Yet leaders can be made in the sense that anyone, given *only*

ability, can learn to order the actions of others efficiently, and to command their loyalty and cooperation. That is one reason why it is so necessary for interns, residents, and younger physicians to establish a firm grasp of the fundamentals in medicine at this stage of their training, particularly in the basic sciences. For it is in Army hospitals and other medical installations that the medical leaders of tomorrow are developed. It should always be remembered that there is strength in knowledge. Complete knowledge of one's profession is an essential key to leadership.

In some countries men are born to lead in a different sense. In the few places in the world where feudalism still lingers, the aristocrat leads both in peace and in war. The English word "gentleman," meaning "of a higher caste," has now lost its original meaning. Washington and Lee represented this type of leader, drawn from the landed aristocracy that the United States almost developed in the South prior to the Civil War. They were doubly fortunate. In addition to undoubted natural endowments, the families into which they were born ensured advancement.

This discussion is not concerned with the selection of a leader, but with the leader's actions after selection. How to be chosen is a different story, and sometimes not a pretty one, if told candidly. Lincoln selected and tried out many commanding generals before he picked the real leader—Grant. What is discussed here is conduct *after* being chosen—how to be a successful leader; for there are principles by which a leader can guide himself to advantage. Since my life has been spent in the military service, it is quite natural that these suggestions should be based on military observation; but I believe they are applicable wherever one man is placed above another. I do not necessarily mean highly placed—for the same principles apply to the ward officer in the hospital, the senior resident, and the noncommissioned officer, as well as to those in higher echelons of responsibility.

The one quality a leader *must* possess is *ability*. In contrast to Washington and Lee, Grant brought to the office of Commanding General of the Army of the United States nothing *except* his ability. His appearance was unimpressive, and he came from an undistinguished family. He was careless in his dress; silent and solitary in his habits. Even his classmates at West Point had difficulty in recollecting him in later years, even at that time, when classes at the U.S. Military Academy were small. There were 39 members in Grant's graduating class, whereas today classes are in the neighborhood of 600.

No one knew Grant at the outbreak of the Civil War. His appli-

cation for service was pigeonholed in Washington and forgotten. The Governor of Illinois, who badly needed men of military experience, put Grant to filling out forms. General Halleck, his superior officer, took one look at his unimpressive figure and turned contemptuously away, rejecting a plan that later led to Grant's first great victory. This was his attack and capture of Forts Henry and Donelson, which retained Kentucky and probably Missouri in the Union, resulted in the occupation of Tennessee, and opened the Mississippi River as far south as Vicksburg. Grant was no born leader; he made himself.

It is noticeable that Grant's lack of family and personality affected only his being selected for command. Once appointed, he had no difficulty in holding the confidence and loyalty of his staff, his generals, and his troops. So, given ability and the opportunity, there is no reason why anyone cannot lead others, in the hospital, on a construction job, in an office, on the athletic field, or even on the field of battle.

I have listed 10 suggestions that I believe cover the basic principles of leadership:

The first is very simple. "*Be yourself.*" At some time or other everyone has had leaders in school, business, or in the military pointed out as examples to follow. Conscious imitation always defeats itself, is invariably evident, and usually does not serve the purpose intended. To be sure, desirable qualities may be absorbed unconsciously. Thus, by associating with cultivated people a person may acquire culture; if his associates speak good English he may do likewise, particularly if he is young. To this type of imitation, of course, there is no objection. When the imitation becomes conscious, however, it is exposed as false. It is said that Grant's carelessness in his dress was a deliberate imitation of General Taylor, under whom he had served in Mexico, and for whom he had great admiration. If so, the habit did not contribute to Grant's greatness. Perhaps it is more accurate to say that Taylor's slovenliness became an excuse for Grant to indulge his own.

A second quality that I believe very desirable is *equanimity* or *self control.* It can, to a certain extent at least, be acquired.

A Confederate colonel called to his fleeing men, exclaiming, "There is Jackson standing like a stone wall!" General Jackson was human, and the Confederate flank was falling back; it was the first major battle of the Civil War. I suspect that Jackson felt fear. Yet externally he was calm and collected, unshaken, and to the disorganized troops near him, truly a stone wall in strength. This quality is sometimes lacking in able and successful men—they are often nervous, irascible, even bad tempered—but such men are successful in spite of

their failings, not because of them. The natural reaction of a subordinate when such a display of emotion takes place is to acquire an impression of weakness and unreliability.

Impartiality and *justice* are not similar qualities, but are allied in their effects.

A leader cannot afford to be too intimate with those he leads, because he must be impartial and he must be just. Where some of his subordinates are personal friends and some are not, it is nearly impossible to be impartial. However, for successful leadership this facet of human nature must be overcome as much as possible. Where intimacy exists, partiality will always be alleged by those passed over or rebuked, whatever be the real cause. One of the penalties of leadership is loneliness; the higher the leader's rank the fewer must be his friends and intimates. It is most difficult to achieve a balance between too great formality and too great familiarity. A leader should not be pompous or isolated and yet he cannot be more intimate with one than with another, and those who seek his society through self interest must be discouraged.

Perhaps these qualities are more important in the Army than elsewhere. However, they exist in all walks of life. I believe that they are responsible for the perpetuation in the military of that very un-American institution—the social gulf between the officer and enlisted men. This gulf originated long ago when officers and enlisted men came from different social castes, though this certainly is not true today. The gulf remains to some extent, however, because the officer is not only the professional leader of the soldier, he is also his disciplinarian, the arbiter of his conduct and morals, and he may even sometimes have to order duty dangerous to life. Impartiality is, therefore, an essential of leadership. Even in civilian life there is no good effect when the friend of the boss is advanced to a higher position with more pay, and candidates with better qualifications are passed over.

As previously mentioned, impartiality and justice are not the same; one can be impartially unjust. But justice needs no discussion; no man can hold the loyalty of others while being deliberately unjust.

Demand results, not methods—for 2 reasons. In the first place, results are easier to order and easier to inspect. In the second place, when exact methods are prescribed, a subordinate can be held responsible only for compliance with them, and not for the end desired. Moreover, in order to develop subordinate leaders responsibility must be delegated.

I might add a third reason: Many minds working independently toward the same objective are likely to develop better methods than

those prescribed from above. Better methods found by one are quickly recognized and adopted by others, when they are free to do so. A leader should not hesitate to use the brains of his subordinates.

Assume loyalty until disloyalty is proved. I know of no quicker way to destroy the spirit and efficiency of an organization than by constant spying and suspicion. It is far better to endure a few seditious ones and grumblers than to adopt the opposite policy.

Too much must not be expected in the way of loyalty; certainly not the type demanded in medieval times when subjects and subordinates swore allegiance to the king. On the old Army efficiency report form there was a statement regarding loyalty that applies in civilian life as well as in the military: "Proper authority having decided the procedure to accomplish a certain end, does he render willing and generous support regardless of his personal views?" That is enough. Argue with the "boss" before the decision is made—but once made, it should be abided by and supported.

Avoid mass punishment and threats. There are many examples of the mass punishment concept outside of the military, such as certain city ordinances, traffic laws, and factory regulations. Because one man may steal the company's time, all must punch the clock. Members of an entire organization should not be penalized because of the faults of a few. This is usually a sign of weakness in a leader who is afraid to seek out and bring the actual offenders to task. I think it a real test of leadership to have the courage to confront individuals with their delinquencies personally. It is far more pleasant for the leader to say "yes" instead of "no," but the "noes" must be said and the leader must take the responsibility of saying them.

I have had the unhappy experience of serving under 1 or 2 people in the military service who were unable to issue an order without naming a penalty at the same time. A feeling of antagonism is almost instinctive toward such men. I am convinced that the quality of leadership is almost inversely proportional to the number of orders issued. I further believe that every leader should strive to have his subordinates carry out his wishes because they feel that they are just, logical, and to the best possible interests of all concerned. When leadership operates on this principle, a wish is usually interpreted as an order and is so executed.

Reward good service, if only by a word or letter. In general, there are only 2 things that make men work hard—the hope of reward and the fear of punishment. In the present-day Army, the latter group is infinitesimal. I use the word "reward" in its broadest sense to include the reward of accomplishing a mission, such as Walter Reed's feeling of personal reward in having found the cause of yellow fever and Dr.

Salk's in developing a successful vaccine against poliomyelitis. Most men expect to be complimented when they have done a good job, and do not resent being informed in private, constructively, when they have not performed up to their expected capabilities.

Give reasons and objectives. Everyone does a better job in civilian or military life when he is told why something has to be done. In military service, particularly in war, time does not always permit this to be done. However, most missions are better and more enthusiastically performed when reasons are explained in advance, and this should be done whenever feasible.

Courtesy and sympathy towards subordinates are absolutely essential and too often neglected. Do not be afraid to be a gentleman. Politeness is one of the cheapest commodities, yet I know of no other quality that pays bigger dividends. The personal rights and dignity of subordinates must be guarded and preserved as though they were the leader's own.

Many of these attributes are desirable but not essential. However, there is one quality no successful leader can do without. Above everything else, he *must know his trade.* Nearly everything else can be dispensed with, but never that. A real leader must convince everyone in his particular organization that no one in that organization can do the job as well as he himself. There is no substitute for knowledge and ability.

Grant was a successful leader of troops because he knew his business as a general. But when he turned to politics and business, things of which he knew nothing, he became the dupe of self-seeking politicians and dishonest business men; not the leader, but the led.

To these 10 fundamental elements of leadership I might add 2 additional ones. They are *humility* and *belief in a Supreme Being.* These 2 additional attributes have been predominant in the really great leaders of all time.

In the early 1800's two men were born in the United States, one in Kentucky and one in Virginia. The former moved to Illinois and from then on was identified and associated with that state. The latter was from birth to death identified with the State of Virginia. I believe that if each of these 12 principles were applied, individually and collectively, to Abraham Lincoln and Robert E. Lee, their respective ratings on any poll would be 100 percent. In my opinion, they were the greatest leaders that this, or any other country, has ever produced.

A thorough understanding of the basic principles of leadership, and constant striving to follow their precepts, will help produce the desired leaders of the future, and effectively disprove the old saying, "Leaders are born—not made."

Clinical Use of the Secretin Test

COLONEL JAMES T. HARDY, USAF, MC

DISEASE OF THE PANCREAS is difficult to diagnose in its early stages. Because of its retroperitoneal position this organ is not easy to palpate; and because of its high degree of reserve a good portion must be involved before definite clinical signs and laboratory abnormalities become apparent. Pathologic changes may be far advanced, therefore, before a clinical diagnosis of pancreatic disease can be made.

In 1902 Bayliss and Starling[1] discovered in the duodenal mucosa a hormone, secretin, that caused the pancreas to secrete a large amount of juice, poor in enzymes, amylase, lipase, and trypsin. Chiray and co-workers[2] were the first to take advantage of this discovery by devising a test of external pancreatic secretion for the study of pancreatic function. Hammarsten and co-workers,[3] Agren and his associates,[4, 5] and others [6–8] followed with valuable investigations. More recently Lake,[9] Grossman,[10] and Dreiling and his group[11–19] have made extensive and important contributions to this subject.

PROCEDURE

Technic

The technic of the secretin test used by the writer is as follows:

The patient is allowed to eat his usual dinner the night before the test but nothing else is permitted until the test is completed the following day. The positioning of the tube is accomplished by the technic described by Raskin and co-workers,[20] with minor modifications. At approximately 7:30 a.m. the patient swallows the double lumen Diamond tube to the 45 cm mark. He is then placed on his left side with the head of the bed elevated to approximately 35°. After 10 additional cm of tubing is allowed to pass, the patient is asked to sit on the edge of the bed, lean well forward, and take 3 deep breaths. Then, continuing to lean forward, he turns to the right in the head-down position at the same 35° angle. This maneuver permits the tip of the tube to swing anterior to the spine to the right side, where it is in position to pass through the antrum into the duo-

From the Gastroenterology Service, U.S. Air Force Hospital, Lackland Air Force Base, Texas.

denum. With the patient on his right side in the head-down position, he is instructed to swallow the tube slowly, at the rate of about 1 cm per minute.

After approximately 70 cm of tubing has been swallowed, the patient is taken to the fluoroscopic room and the position of the tube is checked. In most instances the tip will be found in the duodenum, approaching the ligament of Treitz. If the tube is coiled in the stomach, it will be necessary to withdraw it until the tip is at the most dependent portion of the stomach. The patient must then repeat the maneuver of sitting on the edge of the bed, bending forward, taking 3 deep breaths, and lying on his right side with head down. The position of the tube may have to be rechecked several times before it is finally in its proper place—that is with the tip at the ligament of Treitz. In this position the gastric openings can be seen in the stomach and the duodenal openings in the second and third portions of the duodenum (fig. 1).

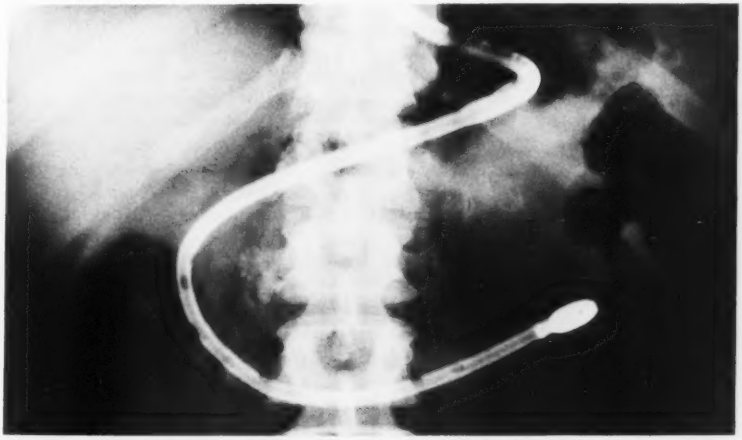


Figure 1. Gastroduodenal tube in proper position.

The patient is then returned to his bed and instructed to lie on his back, shifting position slightly from time to time as necessary to avoid fatigue. The 2 proximal lumens of the tube are then connected to separate bottles marked *gastric contents—control* and *duodenal contents—control*. The standard suction machine is set for a negative pressure of approximately 120 mm of water. With constant suction maintained, control specimens are obtained for a period of about 15 minutes. Suction is discontinued, clean specimen bottles are connected, and 1 unit of secretin per kilogram of body weight is administered intravenously. Suction is then continued.

Almost at once an increase in the flow of duodenal fluid can be noted. From the time of the intravenous injection of secretin the specimen bottles collecting the duodenal and gastric juices are changed at 10-, 20-, 40-, and 60-minute intervals. At the conclusion of this 1-hour period a specimen of blood is drawn for amylase determination. A roentgenogram of the abdomen is made to confirm

and record the proper position of the tube. The tube is then removed and the patient allowed to return to his room. At the 2-hour period from time of injection of the secretin another blood sample is drawn for amylase determination. Following this the patient is allowed to resume his previous diet.

Laboratory Determinations

The 5 specimens each of gastric and duodenal contents, properly labeled as to source and time, are then sent to the laboratory. Determinations for volume, pH, bicarbonate, occult blood, and sometimes icterus index are performed on each of the duodenal specimens; and for volume, pH, free hydrochloric acid, and occult blood on each of the gastric specimens. Amylase determination [21] is performed on the total pooled duodenal specimens.

The pH may be determined by means of hydrion paper, icterus index by the usual potassium bichromate comparison method, occult blood by the guaiac test, free hydrochloric acid by the usual tenth-normal sodium hydroxide titration technic. The bicarbonate determination can be done in either of 2 ways: The Van Slyke procedure is standard but a little more difficult for the small laboratory with less experienced technicians; the titration technic [22] is easily carried out, requires a minimum of equipment and apparatus, and gives accurate results. Hawkins and Osgood [23] have shown that the results of the Van Slyke and titration technics are comparable. I have used the latter with very good and reproducible results.

The pH determination is important in that it might show contamination of duodenal contents with gastric contents or vice versa. The gastric specimens should all have a pH below 7, the duodenal specimens a pH above 7. This of course may not hold true in achlorhydria. The presence or absence of occult blood in the specimens may be of importance when bleeding lesions of the upper gastrointestinal tract are suspected.

The volume, bicarbonate, and amylase depend upon the integrity of the pancreatic parenchyma and ducts. Since secretin does not stimulate the pancreas to produce enzymes, the amylase present is thought to represent merely a washing-out of that present within the ducts. Volume may be diminished in marked destruction of parenchymal cells or in ductal obstruction. A decrease in bicarbonate concentration, on the other hand, usually indicates parenchymal disease.

For normal values the standards of Dreiling [11] have been adhered to and my results conform quite closely with his. In 60 minutes the total volume of duodenal fluid should be at least 102 ml or 1.7 ml per kilogram of body weight. The bicarbonate should be at least 91 mEq per liter in at least 1 of the 4 postsecretin specimens. The amyl-

ase should be at least 2.9 units per kilogram of body weight or 173 units per 100 ml of total duodenal specimens.

CASE REPORTS

CASE 1. A 39-year-old slightly obese white woman had had intermittent right upper quadrant pain for about 8 months, at unpredictable times but thought to be worse after eating. Physical examination revealed no abnormalities other than slight tenderness in the right upper quadrant. Roentgenograms of the gastrointestinal tract were normal. The gallbladder roentgenograms were interesting in that the viscus was rather large and a little fainter than expected, and did not contract within a 2-hour period following the fatty meal (fig. 2). No stones were seen. A secretin test gave the results shown in table 1.

Figure 2 (case 1). Gallbladder 2 hours after a fatty meal.

At operation a fibrous stricture of the sphincter of Oddi was incised and immediately a great gush of fluid issued from the duct. Routine cholecystectomy and sphincterotomy were then performed. The patient made an uneventful recovery and 3 months later was entirely asymptomatic.

Comment. The total volume of duodenal fluid in this case was considerably diminished. Bicarbonate was also diminished in all specimens, the maximum being 70.2 mEq per liter. Note also that the 1-hour serum amylase was 240 units per 100 ml and the 2-hour amylase 255 units per 100 ml. The impression preoperatively was that this patient had chronic pancreatitis. This case represents one of ductal obstruction without apparent disease of the pancreatic parenchyma; at operation, at least, the pancreas appeared grossly normal. We see, however, that the volume and bicarbonate were both diminished. The elevated 1- and 2-hour serum amylase may have resulted from pancreatic stimulation in the presence of ductal obstruction. This will be discussed in more detail later.

CASE 2. A 60-year-old white man began to lose weight 6 months before admission. The diagnosis of diabetes mellitus was made. Diarrhea of 6 stools per day was noted; the stools were described as light in color and bulky. Weakness progressed. On admission to the hospital, examination revealed evidence of weight loss and moderate ascites, with no other abnormalities. Roentgenograms of the gastrointestinal tract and gallbladder showed no abnormalities. All clinical laboratory determinations were normal, including liver function studies. On peritoneoscopy the peritoneum, liver, and observed loops of bowel were normal. A secretin test gave the results shown in table 1.

The patient continued to deteriorate and subsequently an elevated sedimentation rate and sulfobromophthalein (Bromsulphalein) retention developed. At no time did he have pain or anemia. He died 1 year after onset of his original weight loss. At autopsy right hydrothorax and left pleural thickening and adhesions were found. There was marked destruction of the body and tail of the pancreas by carcinoma, with metastases to the peritoneum and ileum.

Comment. Note that the total volume here was only 64 ml, the maximum bicarbonate concentration 46.8 mEq per liter. Serum amylase was 20 units at 1 hour and 40 units at 2 hours. Because of the patient's age, history, and lack of pain the diagnosis was thought to be carcinoma rather than pancreatitis. It may be that the markedly diminished serum amylase was indicative of pancreatic destruction. Certainly the low volume and bicarbonate reflect this destruction.

CASE 3. A 46-year-old white man had hepatitis in 1941. In 1953 he had an episode of acute abdominal pain diagnosed as hepatitis. A liver biopsy at that time showed cirrhosis. The following year hemochromatosis was suspected, but a skin biopsy failed to confirm this diagnosis. In 1955 a liver biopsy was reported

Table 1. ***Duodenal fluid and serum amylase in 6 patients after intravenous secretin stimulation***

Case	Weight (kg)	Diagnosis	Time (min)	Duodenal fluid Volume (ml)	Expected volume max/min (ml)	pH	Bicarbonate (mEq/l)	Serum amylase (units/100 ml) 1 hour	2 hours
1	72	stricture of sphincter of Oddi	control	9		7	32.4	240	255
			10	14		8	44.0		
			20	5		8	44.0		
			40	2		6	42.2		
			60	25		8	70.2		
			Total	46	/122				
2	70	carcinoma of pancreas; diabetes mellitus	control	10.5		6	22.4	20	40
			10	19.0		7	36		
			20	13.5		7	38.6		
			40	11.5		7	42.2		
			60	20.0		7	46.8		
			Total	64.0	/119				
3	74	hemochromatosis	control	36		7.5	6		
			10	109		8	42.2		
			20	78		8	46.6		
			30	102		8	48.6		
			40	146		8	48.6		
			60	141		7.5	40.4		
			Total	576	125/281				
4	63	nontropical sprue	control	66		8	42.2	165	20
			10	13		8	48.6		
			20	7		9	82.8		
			40	78		9	136.8		
			60	86		9	136.8		
			Total	184	/107				
5	78	abscess of pancreas; diabetes mellitus	control	18.5		5	7.2	167.5	160
			10	22.5		7	16.2		
			20	7		7.5	27.8		
			40	10		7.5	30.6		
			60	10		7.5	36		
			Total	49.5	/132				
6	63	pancreatic calculi; diabetes mellitus	control	30		6	2	105	120
			10	21		8	16.6		
			20	7		8	25.6		
			40	15		8	26.5		
			60	20		8	26.5		
			Total	63	/107				

562174 O—60——2

as positive for iron. A diagnosis of hemochromatosis was made. During the 2 years before admission, the patient had been receiving phlebotomies as treatment for his hemochromatosis and was relatively asymptomatic.

On admission physical examination revealed blue-gray skin, large hard liver, sparse hair, hypertrophic breast development, atrophic testes, and severe esophageal varices. Clinical laboratory procedures and liver function studies revealed no abnormalities. A liver biopsy showed severe fibrosis and iron deposits characteristic of hemochromatosis. An oral glucose tolerance test failed to reveal evidence of diabetes mellitus. Since the glucose tolerance test gave no evidence of pancreatic endocrine dysfunction, a secretin test was performed. Results are shown in table 1.

Comment. Note that the volume, 576 ml, was high, the bicarbonate low, the maximum being 48.6 mEq per liter. Although this undoubtedly represents some abnormality of the pancreas, its exact significance is unknown at this time. Similar results of the secretin test in hemochromatosis have been recorded by Althausen and co-workers.[24]

CASE 4. A 21-year-old white man had been in good health until the age of 6 years, when he began to have recurrent bouts of pneumonia at yearly intervals. Since age 15 he had been essentially free of respiratory symptoms. During the same 9-year period, he had experienced frequent bouts of diarrhea and vomiting, which seemed to be increased by fatty foods, green vegetables, and cereals. His stools were light in color and floated on water. He stated that he passed excessive gas by mouth and rectum. The patient had been underweight and lacking in energy all his life. A diagnosis of nontropical sprue was made during his teens, and the patient was treated with iron, vitamin B_{12}, calcium, folic acid, and multivitamins. He made a remarkable improvement and was doing quite well until 3 months before admission. He had stopped taking the aforementioned medication and was eating a more liberal diet, including fats and cereals. Abdominal discomfort and steatorrhea had reappeared.

Physical examination revealed a tall thin man with protuberant abdomen. There was moderate diffuse abdominal tenderness, and the feces noted on the rectal glove were yellow and creamy. Significant clinical laboratory findings were serum carotenoids of 14 micrograms per 100 ml (normal 80–120 mcg/100 ml) and 5-hour urinary excretion of 3.5 grams of D-xylose (normal greater than 5 grams in 5 hours after ingestion of 25 grams). Roentgenograms showed puddling and segmentation of barium in the small intestine. The results of a secretin test are noted in table 1.

Comment. Though the laboratory tests and reontgenograms pointed to malabsorption, as in nontropical sprue, the history of frequent respiratory infections in childhood raised the question of cystic fibrosis of the pancreas. The total volume and maximum bicarbonate concentration—184 ml and 136.8 mEq per liter—were well within normal. Correlated with the other findings, this permitted us to rule out the pancreas as the cause of this patient's steatorrhea and to make a diagnosis of nontropical sprue. This case illustrates the value of the

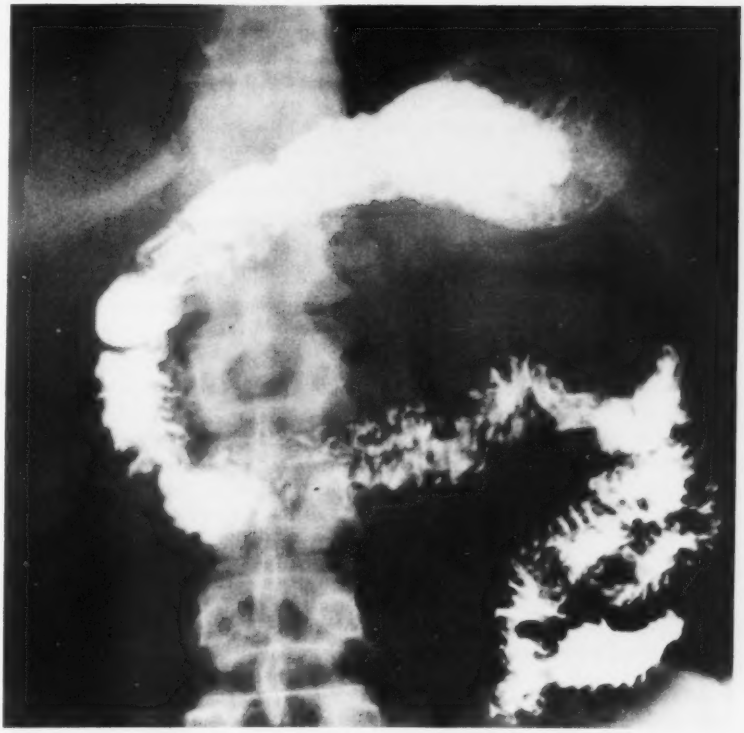


Figure 3 (case 5). Upper gastrointestinal series. Pressure defect in stomach, with enlargement of duodenal C-loop.

secretin test in helping to distinguish pancreatogenic from non-pancreatogenic steatorrhea.

CASE 5. A 50-year-old white man had been a consistent imbiber of alcoholic beverages for many years. Nine years before admission he began to have epigastric pain, and a diagnosis of duodenal ulcer was made. Although his pain continued intermittently, he had no acute episodes requiring hospitalization. One month before admission mild diabetes mellitus was discovered. On the night of admission the patient had awakened from sleep with severe epigastric pain.

Examination on admission revealed rather severe abdominal tenderness and an ill-defined midabdominal mass. A diagnosis of pancreatitis was borne out by markedly elevated serum amylase during the first 2 days of hospitalization. This rapidly returned to normal, however, and was unaccompanied by other laboratory abnormalities. After convalescence was well in progress, roentgenograms of the upper gastrointestinal tract revealed what appeared to be a mass pressing on the stomach and increasing the size of the duodenal C-loop (fig. 3). Though the

patient's general condition continued to improve, abdominal tenderness did not subside and the impression that a mass was present remained. A secretin test gave the results shown in table 1.

After 3 months, with a preoperative diagnosis of pancreatic pseudocyst, the patient underwent an operation. The mass, a pancreatic abscess rather than a cyst, was drained, and the patient made an uneventful recovery. Several months following the operation he was completely asymptomatic and diabetes mellitus was well controlled on a small daily dose of insulin.

Comment. The total volume here, 49.5 ml, was considerably diminished. Bicarbonate concentration was also greatly diminished, the maximum being 36 mEq per liter. It was believed that these findings confirmed the presence of pancreatic disease, the clinical diagnosis being pseudocyst resulting from recurrent attacks of pancreatitis. At operation it was a surprise to find an abscess, since several months had elapsed since the patient had had any acute symptoms. The secretin test, however, correctly confirmed pancreatic disease.

CASE 6. A 20-year-old white man was admitted to the hospital with a history of intermittent epigastric pain for 3 years, usually worse at night, unrelieved by antacids, but improved by doubling up in a sitting position. He had had mild diabetes mellitus for 10 months. During the month before hospitalization his epigastric pain had been severe and frequently accompanied by nausea and vomiting. The diabetes was easily controlled with a small daily dose of insulin.

Physical examination revealed moderate epigastric tenderness. No masses were felt. Routine laboratory work revealed no abnormalities. A roentgenogram of the abdomen showed multiple opacities in the region of the pancreas, having the appearance of pancreatic calculi (fig. 4). Roentgenograms of the upper gastrointestinal tract were normal. A secretin test gave the results shown in table 1.

At operation many stones were removed from the pancreatic ducts. Distal

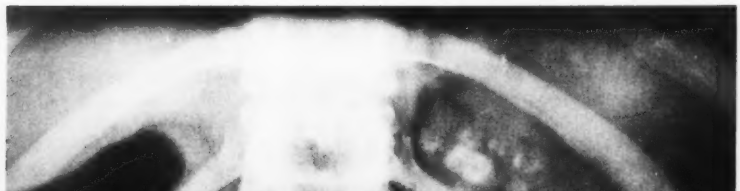


Figure 4 (case 6). Calcification in area of pancreas.

pancreatectomy and pancreaticojejunostomy were performed. The patient had a rather stormy immediate postoperative course but improved rapidly and made an uneventful recovery. Several months following operation he was asymptomatic, and diabetes mellitus was well controlled on 25 units of insulin per day.

Comment. The total volume, 63 ml, was markedly diminished, as was the maximum bicarbonate concentration, 26.5 mEq per liter. This led to the conclusion that the patient had suffered from recurrent pancreatitis and that the radiographic opacities were indeed pancreatic calculi. Operation confirmed this diagnosis and the validity of the secretin test.

DISCUSSION

The foregoing cases illustrate a variety of conditions in which secretin tests can be of help in deciding whether the pancreas is the source of the difficulty. If the test is abnormal, we can feel reasonably sure that there is trouble in the pancreas or its draining ducts. A normal test, however, does not rule out pancreatic disease. In view of the reserve that this organ possesses, it is no surprise that there should be considerable destruction or disease before an abnormal result is obtained.

The response to the intravenous administration of secretin depends upon two things, the integrity of the pancreatic parenchyma and the patency of the pancreatic ducts, and varies with the degree of parenchymal damage and ductal obstruction. With minimal to moderate parenchymal damage and no compromise of ductal patency, bicarbonate concentration is diminished and volume is normal. With marked parenchymal damage both volume and bicarbonate concentration are diminished. If there is significant ductal obstruction with minimal parenchymal damage there is diminution in volume but not in bicarbonate concentration.

Abnormal results do not give a definite etiologic diagnosis, but merely tell us that the function of the pancreas is compromised. The clinical history along with an abnormal test, however, often permits us to make a definite etiologic diagnosis. Certain clues within the results of the test itself have been found by some workers to be statistically significant in arriving at an etiologic diagnosis. For instance, Dreiling [13] has found that in carcinoma of the pancreas the volume is most apt to be diminished, although the bicarbonate concentration may continue at a normal level. His investigations [14] reveal that chronic pancreatitis causes a diminution in bicarbonate concentration though the volume may remain normal for a longer period. It can easily be seen, however,

that with sufficient disease in the pancreas both values will be diminished.

Since the enzymes are secreted in proportionate amounts in response to intravenous secretin administration, it is convenient to determine only amylase in the duodenal fluid. Dreiling [25] points out that after secretin the concentration of this enzyme in pancreatic juice varies inversely with the rate of flow, the rate of enzyme secretion being unaltered. The important determination, then, is the total enzyme secretion, which may be decreased in pancreatic duct obstruction or in parenchymal disease of the pancreas. I have found the duodenal amylase determination to be the least valuable of all in the secretin test; seldom is it abnormal. I have usually found it normal in the face of markedly diminished volume and bicarbonate concentrations. For this reason, my conclusions have always been based on the total volume output and the bicarbonate concentration.

The level of serum enzymes following secretin injection has received attention from a number of workers. Studying serum amylase and lipase concentrations in normal controls and in patients with various types of pancreatic disease, Lopusniak and Bockus [26] found no elevation in pancreatic serum enzymes in 18 control patients after secretin injection. Following attacks of pancreatitis, elevated serum enzymes rose further under secretin stimulation. For as long as 10 weeks, in patients in whom the serum enzyme level had returned to normal, serum enzymes increased after secretin. In patients with evidence of marked pancreatic insufficiency such as steatorrhea, calcification, and diabetes, secretin stimulation produced no increase in serum enzymes. In patients with proved carcinoma of the body of the gland the response was negative, whereas in 2 patients with carcinoma of the head of the pancreas a marked rise in one or both serum enzymes followed secretin administration. This rise supposedly represented ductal obstruction, in the presence of which pancreatic stimulation caused elevation of serum enzymes.

Sun and Shay [27] also believe that the determination of serum enzymes following intravenous secretin stimulation is of definite value. They have found an increase after acute episodes of pancreatitis and also in proved pancreatic carcinoma. On the other hand Shingleton and associates [28] found significant elevation of serum amylase after secretin in 2 of 32 control patients and in only 1 of 11 patients with chronic pancreatitis. No significant change occurred after secretin and bethanechol (Urecholine) chloride injection in a control series of 14 patients, or in 6 patients with chronic pancreatitis. Of 4 patients with pancreatic cancer, 1 showed a rise in amylase. On the basis of these results these investigators believed that serum amyl-

ase determination was of little value in diagnosis of these conditions.

Dreiling [25] has pointed out that most series show overlapping of data and that disparate findings have been reported by many observers. In his series [19] of 192 patients studied with combinations of secretin, methacholine (Mecholyl), bethanechol chloride, and morphine, the blood amylase responses could not be correlated with the known state of pancreatic function as determined by operation or secretin test. Although Dreiling referred to blood amylase, Sun and Shay [27] and Lopusniak and Bockus [26] found that lipase was the serum enzyme more often found abnormal after secretin injection.

My own experience leaves me without any firm conviction on the significance of serum amylase levels. The patient in case 1 was proved to have rather severe obstruction at the sphincter of Oddi and had shown an appreciable elevation of serum amylase at the 1- and 2-hour periods following intravenous secretin. On the other hand, in case 2, the patient had a very low serum amylase at 1 and 2 hours following intravenous secretin and at autopsy showed marked destruction of the pancreas by carcinoma. Other patients have had elevated serum amylase after secretin, but opportunity to confirm or deny ductal obstruction has not presented itself in a sufficient number to permit me to draw conclusions. To date I am unwilling to make a diagnosis of pancreatic disease solely on the basis of elevated serum amylase following intravenous secretin.

The secretin test should not be done in patients with suspected acute pancreatitis. During the acute phase blood amylase determinations are far safer and more practical as a means of making the diagnosis and of following the patient. Accepted principles of treatment of acute pancreatitis dictate that stimulation of this organ should be avoided during a period of acute inflammation; therefore, the intravenous injection of secretin is contraindicated. The test is often of value, however, after convalescence is well established. A week or so after the acute episode the test may be abnormal, revealing that the acute episode was indeed due to pancreatitis. Dreiling [14] has pointed out that the secretin test may be of value as a prognostic sign following acute pancreatitis and that abnormal responses obtained several weeks after all clinical findings and symptoms subside indicate persistent inflammation and possible chronicity.

Abnormal secretin response is almost always encountered in patients with chronic pancreatitis. This is manifested by depressed bicarbonate concentration; the volume and amylase secretion may be normal or less markedly decreased. It would appear that suspected chronic pancreatitis is the indication par excellence for the pancreatic secretin test. Chronic or recurrent abdominal pain for which no

ready explanation is available is a common occurrence in gastroenterologic practice. Though a normal test does not unequivocally rule out pancreatic disease, such a result would be strong evidence against chronic pancreatitis.

Test results encountered in patients with pancreatic tumors depend upon the location and extent of parenchymal and ductal involvement. If a large part of the parenchyma is involved volume and bicarbonate are diminished. If the tumor involves principally the head and consequently the major ducts the volume may be markedly diminished with a normal bicarbonate concentration.[13] Tumors involving only the tail of the pancreas produce no abnormalities in secretin response; insufficient parenchyma is involved and no major ducts are obstructed.

Aktan and Klotz [29] have shown that diabetes mellitus produces no change in the exocrine pancreatic secretion. In a patient with diabetes but with no family history of the disease (cases 2, 5 and 6), however, diabetes on the basis of a pancreatic lesion should be considered and a secretin test should be done.

The patient with hemochromatosis reported here (case 3) had a high total volume of secretion with low bicarbonate concentrations. Althausen and co-workers [24] studied 7 patients with hemochromatosis by means of the secretin test, using the technic and standards of Dornberger and his associates.[30] In 4 subjects the total volume was abnormally high; in 3 of these and in 1 other subject the bicarbonate concentration was abnormally low. This type of response to secretin in patients with hemochromatosis may be characteristic, but is unexplained.

SUMMARY

The technic of the secretin test of pancreatic function is described, and interpretation of the laboratory findings is discussed. Six cases illustrating various types of disease are presented with pertinent comments.

The results of the secretin test depend principally on 2 factors: the patency of the pancreatic ductal system and the integrity of the pancreatic parenchyma. If there is ductal obstruction the total volume of duodenal fluid obtained is decreased. With parenchymal damage the bicarbonate concentration is diminished. Sufficient parenchymal damage even without ductal obstruction results in diminished volume and bicarbonate.

A secretin test should not be done in acute inflammation of the pancreas. The test is most useful in chronic pancreatitis and in carcinoma of the pancreas. The former condition is associated with

decrease in bicarbonate concentration, with less, or later, decrease in volume. The latter condition is accompanied by decreased volume if there is ductal obstruction; when parenchymal destruction is sufficient, both volume and bicarbonate are diminished.

Though the secretin test is relatively time consuming and requires some laboratory support, it is a valuable addition to our methods of investigating pancreatic function and disease and frequently provides the answer to a nebulous clinical situation. Every gastroenterology service should be equipped to accomplish this test.

ACKNOWLEDGMENT: The secretin used in these studies was kindly supplied by Dr. James Hammond, Eli Lilly & Co., Indianapolis, Ind. The technical assistance of Airman first class Jimmy L. Wilkinson and Mrs. Juanita Landez, B.S., is gratefully acknowledged.

REFERENCES

1. Bayliss, M. M. and Starling, E. H.: Mechanism of pancreatic secretion. *J. Physiol.* 28: 325–353, 1902.
2. Chiray, M., Mercier, J. and Salmon, A. R.: Action de la sécrétine purifiée sur la sécrétion externe du pancréas de l'homme. *Bull. et mém. Soc. méd. d. hôp de Paris.* 50: 1417–1426, July 30, 1926.
3. Hammarsten, E., Agren, G. and Lagerlof, H.: Correlation between secretin dose and pancreatic effect in man. *Acta med. scandinav.* 92: 256–266, 1937.
4. Agren, G., Lagerlof, H. and Berglund, H.: Secretin test of pancreatic function in diagnosis of pancreatic disease. *Acta med. scandinav.* 90: 224–271, 1936.
5. Agren, G. and Lagerlof, H.: Pancreatic secretion in man after intravenous administration of secretin. *Acta med. scandinav.* 90: 1–29, 1936.
6. Voegtlin, W. L., Greengard, H. and Ivy, A. C.: Response of canine and human pancreas to secretin. *Am. J. Physiol.* 110: 198–224, Nov. 1934.
7. Diamond, J. S. and Siegal, S. A.: Secretin test in diagnosis of pancreatic disease with report of 130 tests. *Am. J. Digest. Dis.* 7: 435–442, Oct. 1940.
8. Diamond, J. S., Siegal, S. A., Gall, M. B. and Karlen, S.: Use of secretin as clinical test of pancreatic function. *Am. J. Digest. Dis.* 6: 366–372, Aug. 1939.
9. Lake, M.: Diagnostic value of secretin test, including report of 19 operated or autopsied cases with anatomical studies of pancreas. *Am. J. Med.* 3: 18–30, July 1947.
10. Grossman, M. I.: Physiology of secretin. *Vitamins Hormones:* 16: 179–203, 1958.
11. Dreiling, D. A.: Technique of secretin test: normal ranges. *J. Mt. Sinai Hosp.* 21: 363–372, March–April 1955.
12. Dreiling, D. A.: Studies of pancreatic function. Use of secretin test in diagnosis of patients with postcholecystectomy syndrome. *Gastroenterology* 16: 162–171, Sept. 1950.
13. Dreiling, D. A.: Studies in pancreatic function; use of secretin test in diagnosis of tumors in and about pancreas. *Gastroenterology* 18: 184–196, June 1951.

14. DREILING, D. A.: Studies in pancreatic function, use of secretin test in diagnosis of pancreatitis in demonstration of pancreatic insufficiencies in gastrointestinal disorders. *Gastroenterology* 24: 540–555, Aug. 1953.
15. DREILING, D. A. and HOLLANDER, F.: Studies in pancreatic function; preliminary series of clinical studies with secretin test. *Gastroenterology* 11: 714–729, Nov. 1948.
16. DREILING, D. A. and HOLLANDER, F.: Studies in pancreatic function; statistical study of pancreatic secretion following secretin in patients without pancreatic disease. *Gastroenterology* 15: 620–627, Aug. 1950.
17. DREILING, D. A. and LIPSAY, J. J.: Use of secretin test in diagnosis of biliary tract disease. Report of 327 case studies. *Gastroenterology* 17: 242–259, Feb. 1951.
18. DREILING, D. A., DRUCKERMAN, L. J. and HOLLANDER, F.: Effect of complete vagisection and vagal stimulation on pancreatic secretion in man. *Gastroenterology* 20: 578–586, April 1952.
19. DREILING, D. A. and RICHMAN, A.: Evaluation of provocative blood enzyme tests employed in diagnosis of pancreatic disease. *A.M.A. Arch. Int. Med.* 94: 197–212, Aug. 1954.
20. RASKIN, H. F. and others: Diagnosis of cancer of pancreas, biliary tract and duodenum by combined cytologic and secretory methods. I. Exfoliative cytology and description of rapid method of duodenal intubation. *Gastroenterology* 34: 996–1008, June 1958.
21. SOMOGYI, M.: Diastatic activity of human blood. *Arch. Int. Med.* 67: 665–679, March 1941.
22. TODD, J. C., SANFORD, A. H. and WELLS, B. B.: *Clinical Diagnosis by Laboratory Methods: A Working Manual of Clinical Pathology*, ed. 12. W. B. Saunders Co., Philadelphia, Pa., 1953. p. 436.
23. HASKINS, H. D. and OSGOOD, E. E.: Modification of Van Slyke's titration method for estimating alkali reserve of blood. *J. Lab. & Clin. Med.* 6: 37, Oct. 1920.
24. ALTHAUSEN, T. L. and others: Hemochromatosis; investigation of 23 cases, with special reference to etiology, nutrition, iron metabolism and studies of hepatic and pancreatic function. *A.M.A. Arch. Int. Med.* 88: 553–570, Nov. 1951.
25. DREILING, D. A. and JANOWITZ, H. D.: Exocrine pancreatic secretion; effects of pancreatic disease. *Am. J. Med.* 21: 98–116, July 1956.
26. LOPUSNIAK, M. S. and BOCKUS, H. L.: Symposium on pancreatic disease; study of pancreatic serum enzymes following secretin injection in pancreatic affections. *Gastroenterology* 16: 294–308, June 1950.
27. SUN, D. C. and SHAY, H.: Value of combined study of serum enzymes and duodenal contents after secretin in diagnosis of diseases of pancreas. *Gastroenterology* 32: 212–231, Feb. 1957.
28. SHINGLETON, W. W., ANLYAN, W. G. and HART, D.: Diagnosis of pancreatic disorders by certain laboratory procedures. *Ann. Surg.* 136: 578–584, Oct. 1952.
29. AKTAN, H. S. and KLOTZ, A. P.: Fat absorption and pancreatic function in diabetes mellitus. *Ann. Int. Med.* 49: 820–828, Oct. 1958.
30. DORNBERGER, G. R., COMFORT, M. W., WOLLAEGER, E. E. and POWER, M. H.: Pancreatic function as measured by analysis of duodenal contents before and after stimulation with secretin. *Gastroenterology* 11: 701–713, Nov. 1948.

Outbreak of Unidentified Disease in American Personnel in Eritrea

MAJOR JEROME H. GREENBERG, MC, USA
CAPTAIN PERRY W. NADIG, MC, USAR
CAPTAIN DAVID L. ROBERTS, MC, USAR

AN UNUSUAL EPIDEMIC OF DISEASE, initially reported as infectious mononucleosis, occurred in November and December 1958 among some 1,800 United States military personnel and civilian dependents stationed in Asmara, Eritrea, in East Africa. One week before the beginning of this epidemic, an explosive outbreak clinically identified as streptococcic sore throat had occurred. These two outbreaks were viewed with particular interest, not only in themselves, but because of their possible relationship to the unusually high incidence of gastroenteritis and infectious hepatitis that had been in evidence at the station during the preceding year.

BACKGROUND

Eritrea, a former Italian dependency and now federated with Ethiopia, lies adjacent to the Red Sea in eastern Africa, bounded to the north and west by Sudan and to the south by Ethiopia proper. Asmara, the capital, has a population of about 100,000 and is located at the eastern edge of the central Eritrean plateau at an altitude of about 7,000 feet. The climate is temperate, with most of the precipitation concentrated in a rainy season from June to September.

U.S. Army activities centered in Kagnew Station, a modern, well-appointed post located in the outskirts of Asmara. Although the majority of personnel were quartered at Kagnew Station, 180 of the 276 American military families lived off the post in private dwellings in and around Asmara. In addition, 76 U.S. Navy personnel and about a dozen military families lived at an older compound not far

From U.S. Army Hospital, Kagnew Station, Asmara, Eritrea. Major Greenberg is now assigned to Preventive Medicine Division, Office of the Surgeon General, Department of the Army, Washington, D.C.

removed from Kagnew Station. A small group of Army personnel resided at a leased hotel in central Asmara.

In addition to the living facilities, there were a number of work sites located in the surrounding countryside and a leased rest and recreation hotel in Massaua on the Red Sea, some 2 hours distant by car from Asmara.

The dependent children attended school at Kagnew Station and at the time of the epidemics, 258 children were attending grades from kindergarten through twelfth. Because of small numbers of students, the seventh and eighth grades were combined, as were the tenth, eleventh, and twelfth. The teachers were American civilian and military personnel.

EPIDEMIOLOGIC DATA

Before the epidemic under investigation, personnel at Kagnew Station had been experiencing an unusually high incidence of gastroenteritis and infectious hepatitis. The admissions for these conditions among the military population of approximately 1,100 strength are shown in table 1 for each month in 1958. These cases represent only a part of the total incidence, since many individuals with gastroenteritis were not sufficiently incapacitated to require admission to the hospital or quarters. The incidence of these diseases among the nonmilitary seg-

Table 1. ***Admissions for gastroenteritis and hepatitis in U.S. military personnel in Asmara, Eritrea, 1958***

Month	*Gastroenteritis*	*Infectious hepatitis*
January	3	2
February	5	1
March	5	2
April	17	1
May	23	18
June	1	2
July	14	3
August	17	1
September	20	1
October	3	0
November	15	0
December	11	0
Total	134	31

ment of the Kagnew Station population could not be determined satisfactorily because almost all patients with gastroenteritis and many with infectious hepatitis were treated at home.

Approximately 1 week before the beginning of the so-called infectious mononucleosis epidemic, an abrupt outbreak of an illness characterized by fever, sore throat, and polymorphonuclear leukocytosis occurred among the military personnel of the post. Between 3 November and 10 November over 100 persons, almost all of whom ate in the same mess hall, developed this syndrome. Although laboratory confirmation was not obtained, on the basis of epidemiologic evidence it was believed that the outbreak represented beta hemolytic streptococcic disease transmitted through food in the mess. Prompt treatment and prophylaxis with all available forms of penicillin, including benzathine penicillin, was followed by abrupt cessation of the outbreak, with almost no secondary transmission and no sequelae.

On 20 November an 18-year-old soldier living in the barracks was admitted to the hospital with a 2-day illness characterized by fever, sore throat, and follicular tonsillitis. Within the next 3 days tenderness under both costal margins and tender, palpable, axillary nodes developed. Absolute lymphocytosis and atypical lymphocytes were found, and the diagnosis of infectious mononucleosis was made. This same patient had been ill from 8 to 10 November, during the earlier outbreak.

Subsequently, through 20 December, 88 similar cases were reported. In addition, investigation revealed that an earlier case had occurred. The patient (case 1) was a 16-year-old, tenth grade school girl, who had been seen on 28 October because of fever, malaise, generalized lymphadenopathy, and tenderness under both costal margins. Immediately before the girl's illness her young pet gazelle had been ill with diarrhea. The gazelle recovered from this episode but died subsequently, precluding the performance of any studies that might have uncovered a relationship between the human and animal illnesses.

The epidemic involved all segments of the population (fig. 1), but 2 groups, the military medical personnel and the school children in the seventh to twelfth grades, had rates greatly in excess of the other groups (table 2). In the case of the former group, it can be postulated that the increased incidence was directly related to greater exposure within the hospital. The greater incidence in the school children of the upper 6 grades was probably also the result of increased exposure. Figure 2 diagrammatically depicts the discernible relationships among various cases and reveals how case 11, a soldier-teacher who taught in the combined seventh and eighth grades, the ninth grade, and the combined tenth through twelfth grades, may have been instrumental

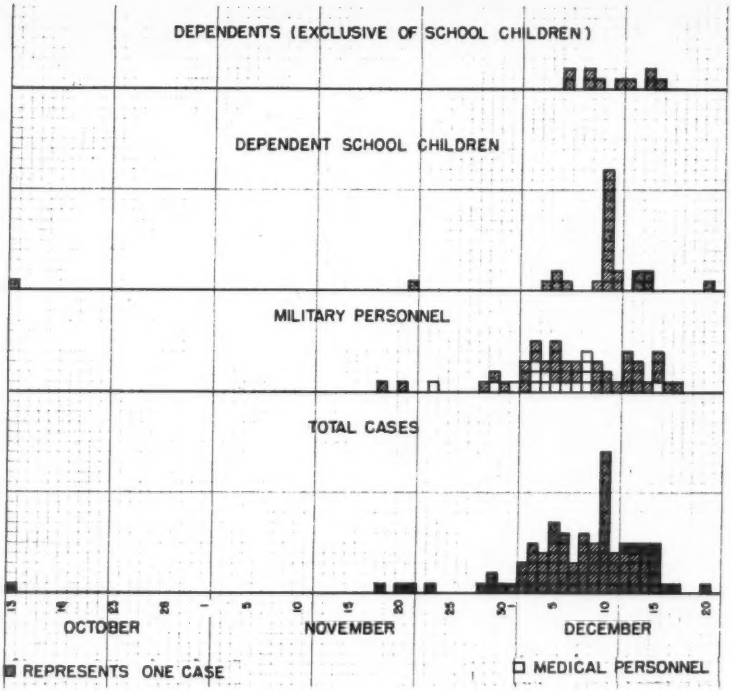


Figure 1. Estimated date of onset of cases, U.S. military personnel and dependents, Asmara, Eritrea, November-December 1958.

in transmitting the infection. It is recognized that many more relationships existed than are shown in the diagram, i.e., among soldiers in the various barracks and worksites and among the school children and other dependents in the course of daily life outside the school. The diagram does emphasize the multiple and intricate relationships that exist within a small, closely knit population.

Figure 2 permits some speculation as to incubation period, the recognizable intervals varying from about 3 to 23 days and averaging 8 to 9 days. In addition, case 61, an eleventh grade girl who became ill on 10 December, had returned from the United States only 5 days before onset, thus establishing at least 1 reliable indicator as to length of the incubation period.

Determination of incidence rates by place of residence (table 3) shows the greatest incidence among military personnel and dependents living in private quarters, both on and off Kagnew Station. This

finding can probably be attributed to the effect of exposure of these people to the school children in their families. The military personnel living in barracks and in the leased hotel had much less exposure to these children and consequently had generally lower rates. A notable exception to this, however, was the medical detachment personnel, whose high incidence undoubtedly stemmed from exposure in the medical facility.

In only 1 of the 54 military personnel who were admitted with the mononucleosis-like disease had the previous diagnosis of infectious hepatitis been made while at Kagnew Station. The hepatitis incidence of 1.8 percent in this group was thus not unlike the general 1958 incidence among the total military population of Kagnew Station—31 cases in approximately 1,125 individuals or about 2.8 percent.

Similarly, the incidence of the mononucleosis-like disease among the military personnel who had been ill during the epidemic of suspected streptococcic disease early in November did not differ significantly from the incidence of the mononucleosis-like disease in the rest of the general military population: 4 of 100 (4%) in the former, and 50 of 1,025 (4.9%) in the latter.

Table 2. ***Incidence of infectious mononucleosis-like disease by military unit or civilian group, Asmara, Eritrea, November-December 1958***

Unit or group	*Population*	*Cases*	*Rate (%)*
Military			
Navy detachment	77	3	3.9
Medical detachment	41	16	39.0
USAMESCA	234	8	3.4
Field Station	300	11	3.7
Operations Co.	393	11	2.8
Guard Co.	78	4	5.1
USAF	2	1	50.0
Total	1,125	54	4.8
Dependents			
School children, under 7th grade	206	1	0.5
School children, 7th–12th grades	52	25	48.1
Other dependents	431	10	2.3
Total	689	36	5.2
Grand total	1,814	90	5.0

It is of interest that the soldier-teacher (case 11) volunteered the information that he had had infectious mononucleosis in college. This was the only report of this kind.

Only 2 concomitant cases of similar disease were reported among native employees, both of whom were domestics. Local civilian health authorities were not aware that any similar illness was affecting the local populace. The general native disease picture at the time was similar to that found in other areas where living standards are low and medical care inadequate. Infections caused by parasites such as hookworm and tapeworm, including Echinococcus, were said to be highly prevalent. Schistosomiasis, smallpox, kala-azar, relapsing fever, and typhus were reported occasionally. Typhoid and other enteric infections, tuberculosis, and venereal disease were undoubtedly frequent.

ENVIRONMENTAL DATA

Investigation of the environment in and around Kagnew Station revealed a number of conditions that were thought to provide possible means of disease transmission. The water supply was derived from a grossly polluted source and treatment was believed to be inadequately

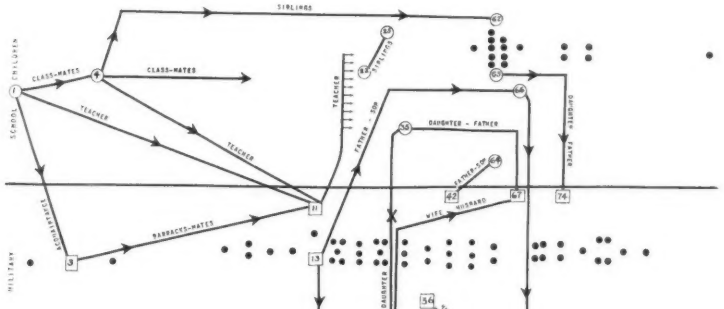


Figure 2. Epidemiologic relationships in outbreak of unidentified disease, Asmara, Eritrea, November-December 1958. Dates are estimated dates of onset. No cases occurred between 13 October and 18 November.

Table 3. ***Incidence of infectious mononucleosis-like disease by place of residence, U.S. military and dependent personnel, Asmara, Eritrea, November-December 1958***

Place of residence	*Population*	*Cases*	*Rate (%)*
Kagnew Main Post			
Barracks	765	32	4.2
Military in quarters	85	4	4.7
Dependents	212	15	7.1
Total	1,062	51	4.8
Tract A			
Navy barracks	62	2	3.2
Military in quarters	11	1	9.1
Dependents	27	2	7.4
Total	100	5	5.0
Off Post			
Military in Belvidere Hotel	22	0	0
Military in quarters	180	15	8.3
Dependents	450	19	4.2
Total	652	34	5.2

controlled. Certain items of food, such as milk and meat, were undoubtedly procured locally by individuals even though this practice was prohibited by military directive. These foodstuffs were of dubious sanitary quality. Even the locally procured fruits and vegetables sold in the Army commissary could not be guaranteed safe, for in spite of surveillance efforts, irrigation with sewage was a distinct possibility.

Native food handlers were employed in snack bars and clubs, though not in the Army mess. The personal hygiene of these personnel as well as of other indigenous employees, including domestics, was questionable. The tendency of the local populace to random defecation undoubtedly provided a constantly available source of infectious material.

Flies were numerous during the period under discussion, and inadequate screening in at least one military club provided access to uncovered foodstuffs. Cockroaches were also numerous. No mosquitoes were in evidence during or after the epidemic. Sandflies were reported to have been absent in American facilities although present elsewhere in the country. Mice were known to infest the commissary warehouse. Rats were not reported.

562174 O—60——3

One of the chief pastimes of personnel at Kagnew Station was hunting. Game included antelope, wart hog, guinea fowl, baboon, hyena, and other wildlife. In addition to providing large quantities of meat for private consumption in homes or public consumption in clubs, this activity undoubtedly also provided ample opportunity for contact with the ectoparasites of the area.

CLINICAL ASPECTS

The 90 recorded cases of the mononucleosis-like disease varied in severity, and undoubtedly many mild and subclinical cases went unrecorded. Table 4 gives the frequency with which significant clinical and laboratory findings were recorded. Because of the explosiveness of the epidemic and the limited medical personnel available, examinations and records were sketchy. Therefore, many of the items listed as "not recorded" may actually have been present with greater frequency.

The most frequent finding was so-called liver tenderness, present in 52 of the 90 cases for which records were available. In 34 cases, however, there was no record of either the presence or absence of such tenderness, and in only 3 cases was a negative statement given. The 1 remaining case was reported only as "liver palpable."

The spleen was reported to be tender in 41 cases, palpable in 5, and negative in 4. In the remaining 40 cases the spleen was not mentioned.

That subcostal tenderness did exist in many cases is certain. Almost every military case and many of the dependent cases were interviewed subsequent to the epidemic and many volunteered the information that they were "sore under the ribs" before the physician examined them.

Adenopathy was a prominent feature, being present to some degree in 55 of 59 cases in which the state of the lymph nodes was reported.

Fever was not a prominent feature. Although significant fever was reported as present in only 9 cases and absent in only 24, the subsequent interview established the fact that fever was not noteworthy in the majority of cases.

Sore throat was reported in only 22 of 25 cases in which a notation was found. However, again the follow-up interview convinced us that sore throat was either absent or insignificant in the other 65 cases.

Almost all patients remarked upon and were most impressed with the marked weakness and fatigue that accompanied the illness. The persistence of this symptom varied. In some cases, this weakness

Table 4. ***Number of infectious mononucleosis-like cases with various findings, Asmara, Eritrea, 1958***

Adenopathy		*Total leukocyte count*	
General	35	Under 5,000	0
Cervical	3	5,000–10,000	17
Axillary	17	Over 10,000	3
None	4	No report	70
No report	31	*Lymphocytosis (highest finding per case)*	
Liver		Under 50%	39
Tender	52	50 to 70%	18
Palpable	1	Over 70%	6
No findings	3	No report	27
No report	34	*Atypical lymphocytes (highest finding per case)*	
Spleen		None	3
Tender	41	1 to 20%	25
Palpable	5	21 to 40%	30
No findings	4	41 to 60%	8
No report	40	Over 60%	5
Temperature		Present but % not specified	2
Over 100°F	9	No report	17
Under 100°F or normal	24	*Heterophil antibodies (nonabsorbed)*	
No report	57	Positive undiluted to 1:16	6
Sore throat		Positive 1:64	2
Present	22	Positive 1:128 to 1:512	3
Absent	3	Positive (titer not specified)	1
No report	65	No report	78

was the only symptom, its presence leading to the discovery of abnormal-appearing lymphocytes in the blood smear and the subsequent diagnosis of infectious mononucleosis.

Laboratory Findings

Unfortunately, the isolation of Kagnew Station, the lack of dry ice in which to ship specimens, and the relatively rudimentary laboratory facilities drastically curtailed the ability to carry out laboratory studies. No isolation studies were performed.

Total leukocyte counts were reported in 20 cases. Of these, 17 were between 5,000 and 10,000 per cu mm and the remaining 3 were over 10,000 per cu mm. Differential counts were reported in 63 cases. In 39 the greatest lymphocytosis was under 50 percent, in 18 it was between 50 and 70 percent, and in the remaining 6 there was over 70 percent lymphocytosis.

In 73 cases blood smears were examined for atypical lymphocytes. The highest finding for each of these is shown in table 4. However, personnel at Walter Reed Army Institute of Research who subsequently examined typical smears did not consider the lymphocytes in question atypical.

The heterophil antibody test had not been previously performed at Kagnew Station and was performed utilizing sheep blood obtained locally. Guinea pig absorption could not be accomplished. For these reasons, little weight was given to the heterophil antibody findings. Subsequently, a group of serums from both convalescent and well persons were tested at Walter Reed Army Institute of Research and found to be negative. The possibility that the 2- to 3-month storage of the serums, even though frozen, adversely affected the heterophil antibody cannot be ruled out entirely.

Three paired serums were screened for evidence of arbor virus and for rickettsial and leptospiral infections at Walter Reed Army Institute of Research. One pair revealed a rise in titer for group A arbor virus from less than 1:10 in the acute phase specimen to 1:80 in the convalescent specimen. All were negative for group B arbor virus, Q fever, the typhus and spotted fever groups, and leptospirosis. The same specimens were tested by agar diffusion technic at the George Washington University School of Medicine, Washington, D.C. for evidence of listeria infection. An initial series of tests were positive, but a second series were negative.

DISCUSSION

Initially it was believed that the mononucleosis-like disease occurring at Kagnew Station was probably of common origin. The relatively explosive beginning of the epidemic, its almost simultaneous appearance in the various population groups, and its rapid disappearance were considered indicative of widespread simultaneous seeding. Furthermore, the water and food supplies had been susceptible to contamination.

The common source hypothesis was entertained in spite of the fact that such a means of transmission of infectious mononucleosis would

be considered most novel and unusual. However, as the data were brought together and analyzed, it became more and more apparent that person-to-person transmission was not only possible, but likely.

Throughout the study there was considerable doubt that the disease in question was infectious mononucleosis. In reviewing the literature on infectious mononucleosis, one is impressed with the divergence of opinion concerning criteria necessary for diagnosis. However, no instances can be found where a group of cases have been diagnosed as infectious mononucleosis in spite of complete absence of positive heterophil antibody agglutination determinations or typical hematologic findings. The presence of one or the other of these has always been reported in a significant proportion of cases.[1-5] In the present epidemic the absence of these findings should rule out infectious mononucleosis as described in the literature, even though the clinical picture was quite similar.

The possibility that the disease in question was of animal origin must be given serious consideration for several reasons. Evidence of listeria infection in 3 serum specimens, though unconfirmed in a second series of tests, directs attention to the sick gazelle associated with the index case. Primarily a disease of animals, listeriosis has been reported as a human infection on numerous occasions, including several where a diagnosis of infectious mononucleosis was made.[6] Numerous other patients had contact with animals in the course of hunting and subsequent preparation of carcasses for eating.

Thus, there was ample opportunity for transmission of disease from animal to man, either directly or by means of insect vector. Once introduced, such a disease might be propagated person to person among a close-knit population such as that of Kagnew Station. However, in the absence of any confirmatory evidence, such an explanation must remain purely conjectural.

Many of the clinical and laboratory features of the disease suggest a virus infection. The possibility was entertained that the disease was an aberrant form of infectious hepatitis. This was supported by some of the observations, including the high incidence of infectious hepatitis before the epidemic and its relative absence during November and December. The clinical evidence of liver involvement reported in a high percentage of cases was compatible with the diagnosis of infectious hepatitis. However, liver function studies could not be performed and no other means was available by which a diagnosis of infectious hepatitis could have been supported.

After the epidemic, a few additional sporadic cases occurred in the next 5 months. After May 1958, however, no further cases were reported. Considerable environmental improvements have been

carried out at Kagnew Station since the epidemic. Possibly as a result of these, not only have there been no additional cases of the unknown disease, but there has also been a marked decrease in the incidence of infectious hepatitis. These reductions in disease have occurred in spite of a rapid turnover in personnel—a practice that constantly adds fresh susceptibles to the population.

In retrospect, it appears that without major effort from outside, and barring serendipity, the identification of unusual or unknown diseases at isolated stations is almost impossible. This is a most unfortunate situation, for golden opportunities for gains in medical knowledge may be slipping by. To exploit an epidemic such as has been described, however, requires rapid and concerted action that is seldom possible unless adequate arrangements exist to permit almost immediate movement of both personnel and materiel.

SUMMARY

In November and December 1958, 90 cases of an unidentified disease occurred among some 1,800 American military personnel and dependents stationed in Asmara, Eritrea. The epidemic followed, by a little over a week, a previous outbreak clinically identified as food-transmitted streptoccocic disease. Clinically the unidentified disease resembled infectious mononucleosis. Although hematologic and serologic studies in Asmara were initially interpreted as confirming the diagnosis of infectious mononucleosis, subsequent tests of specimens in the United States, following several months' storage, were negative.

Initially, the disease was believed to be of common origin because of its explosive appearance among both military and civilian personnel, the presence of sanitary defects, and the history of a high incidence of both gastroenteritis and infectious hepatitis. Subsequent analysis indicates that the disease was spread person to person and that the incubation period averaged 8 or 9 days.

Although laboratory efforts were drastically curtailed by the isolation of the post and the inadequate facilities, some blood specimens were obtained and tested subsequently in the United States. One pair of serums revealed a titer rise for group A arbor virus. All were negative for group B arbor virus and for rickettsial and leptospiral agents. Three pairs gave equivocal results when tested for evidence of listeriosis.

The investigation of the epidemic in Asmara clearly revealed the difficulties inherent in attempting to diagnose unusual entities in isolated areas with inadequate diagnostic facilities.

ACKNOWLEDGMENT: The authors gratefully acknowledge the help of First Lieutenant Chester A. Wiskowski, MSC, USA, U.S. Army Hospital, Kagnew Station, Asmara, Eritrea; Dr. Ross Gauld and Major Edward Buescher, MC, USA, Walter Reed Army Institute of Research, Washington, D.C.; and all other personnel who assisted in the investigation.

REFERENCES

1. Bernstein, A.: Infectious mononucleosis. *Medicine* 19: 85–159, Feb. 1940.
2. Contratto, A. W.: Infectious mononucleosis; study of 196 cases. *Arch. Int. Med.* 73: 449–459, June 1944.
3. Wechsler, H. F., Rosenblum, A. H. and Sills, C. T.: Infectious mononucleosis; report of epidemic in army post. *Ann. Int. Med.* 25: 113–133, July; 236–265, Aug. 1946.
4. Press, J. H., Shlevin, E. L. and Rosen, A. P.: Infectious mononucleosis; study of 96 cases. *Ann. Int. Med.* 22: 546–562, April 1945.
5. Read, J. T. and Helwig, F. C.: Infectious mononucleosis; analysis of 300 cases with 3 characterized by rare hematologic features. *Arch. Int. Med.* 75: 376–380, June 1945.
6. Hull, T. G.: *Diseases Transmitted from Animals to Man*, ed. 2, Charles C Thomas, Publisher, Springfield, Ill., 1955, pp. 241–242.

THE INQUIRING MIND

The spirit of inquiry is a state of mind, just as its opposite is the acceptance of the status quo and the authority of the word, especially the written word. Thus, in the educational institution in which the investigative attitude is strong, yet not divorced from teaching, graduate training is an absorbing and dynamic experience for both instructor and graduate student. If this atmosphere can be maintained alive and thriving, the educational process will not become sterile and, above all, will not become a mere structure of courses and of timid compliance with formal requirements.—Robert A. Kehoe: A New Look at Preventive Medicine in American Industry. *Journal of the American Medical Association*, January 30, 1960.

The Battle of Blood

JOHN G. GIBSON, 2ND, M.D.

BLOOD TRANSFUSION became firmly established as an indispensable therapeutic agent in military medicine during World War II. Plasma proved to be alleviating in the treatment of shock and burns. Concentrated serum albumin was effective, not only as a plasma volume expander, but as a diuretic. But the severely wounded required whole blood, and this need was met by the establishment of the overseas blood program. More than half a million units were made available, by air transport, in combat areas in European and Pacific theaters. Blood transfusion reached the peak of its effectiveness in the Korean conflict.

The first plasma bank in the United States was established by Elliott [1] in 1937, and the first whole blood bank by Fantus [2] in the same year. But it was not until the establishment of Red Cross donor centers during World War II that the feasibility of civilian blood banks became apparent. The return to civilian life of military personnel with experience in the treatment of injured and wounded persons was a great stimulus to the growth of hospital, community, and other blood banks, which in 1956 numbered 2,200, with an annual capacity for collecting, distributing, and administering approximately 5 million units of blood.[3]

About 95 percent of these units are given as whole blood. Yet the requirements of the individual patient are not always met by whole blood. The treatment of severe hemorrhage or of shock may require many liters of blood. But the administration of a single unit of whole blood may jeopardize the life of a patient, through circulatory overloading. In such cases separated red cells are usually well tolerated.[4]

From the Departments of Medicine, Harvard Medical School and Peter Bent Brigham Hospital, Boston, Mass. This article is based, in part, on work supported by grants-in-aid from the National Institutes of Health and contract with the Office of The Surgeon General, Department of the Army, No. DA–49–007–MD610. Presented as a scientific exhibit at the annual meeting of the American Association of Blood Banks at Cincinnati, Ohio, in November 1958.

The indications for the use of plasma in burns, or for correction of deficiencies in clotting factors, are now clear.[5] The beneficial effect of platelets in thrombocytopenia has become firmly established.[6] It therefore becomes imperative that treatment be guided by the specific requirements of the particular patient,[7] thus ensuring the maximum utilization of blood. This is particularly important because blood is always in short supply.

A complete understanding of the use of blood components in therapy requires some knowledge of the development of blood transfusion practices. Many excellent works on blood transfusion have been published.[8-10] These are valuable reference books but they do not emphasize the fact that our present concepts are the result of a continuous development. In casting about for a means of presenting the entire picture as a dynamic growth, it occurred to me that this might be done in a simple manner by treating the discoveries and developments leading up to the modern concept of blood components in therapy as a record of a military campaign: the Battle of Blood.

Figure 1. Medieval surgeon attempting to infuse blood into patient. His transfusion equipment—an animal's bladder and a quill—was forerunner of modern plastic collapsible blood container. (Nouvelle Pratique de Chirurgie, 1691, Michel Ettmüller, Amsterdam.)

Each successful operation met with a temporary check, but every gain served as a basis for the mounting of further attacks, so that the entire campaign, begun in the middle ages, has been a continuing advance.

Blood transfusion could never have become a part of medical thinking had it not been for the classic research of William Harvey.[11] As one point of evidence for the circulation of blood in a closed vascular system, Harvey demonstrated that the cardiac output, over

a period of time, was *always a greater quantity than is present in the whole body.*

Thus was established the concept of the *blood volume.* This was of primary importance, since transfusion therapy is basically aimed at replacement of whole blood lost through hemorrhage or in shock, or of blood components rendered deficient in functional capacity or quantity by trauma or disease.

Attempts in the middle ages to infuse animal (or human) blood were disastrous to both patient and physician because of complete lack of knowledge of compatibility. However, such debacles were not without some gains. Figure 1 illustrates one of these early attempts: The physician, using an animal's bladder as a container and a goose quill as a cannula, is administering blood. This procedure embodied some sound principles: the use of a collapsible air-free container attached directly to the "giving" set, the whole constituting a continuous hemorepellent pathway, and administration by external pressure on the container. This may be considered the forerunner of modern plastic transfusion equipment; but it was to lie dormant for 3 centuries!

The figures that follow are designed to show the many strong points that have been overrun, the coordination of the several movements in a combined attack, and the gradual encirclement and elimination of obstacles to safe and effective blood therapy. The early attempts may be designated as *commando raids*, repulsed with heavy losses (fig. 2).

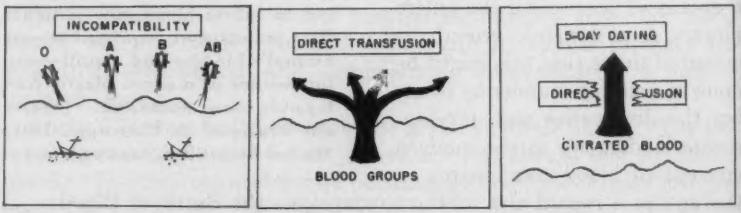


Figure 2. "Commando raids" (*left*). Early failures were due to lack of knowledge of blood compatibility. These may be regarded as commando raids, repulsed with heavy losses by blood group shore batteries. "The beachhead" (*center*). Discovery of blood groups and development of cross-matching technics placed blood transfusion on a firm basis. This advance failed because of limitations of direct transfusion. "The breakthrough" (*right*). Introduction of sodium citrate as anticoagulant made it possible to take blood in one area and give it in another, but the rapid deterioration of red blood cells in sodium citrate renders citrated blood unsafe for more than 5 days.

The discovery of blood groups [12] and the development of typing and cross-matching technics [13–14] placed blood transfusion on a firm scientific basis. We can regard these discoveries as the establishment of a *beachhead* (fig. 2). This advance could not be exploited because of the limitations of direct transfusion technics; [15–17] namely, clotting of donor blood, the risk of sepsis at the operative sites, the obliteration of veins of both donor and recipient, and the hazard of cross infection and communicable disease.

The introduction of sodium citrate as an anticoagulant [18] may be termed the *breakthrough* (fig. 2), because it overcame the limitations of direct transfusions. It was now possible and safe to take blood in one area and give it in another. Citrated blood, fortified with dextrose,[19] was actually used to a limited extent in World War I.[20] Citrated blood made the blood bank a possibility. However, the rapid deterioration of the red blood cell in sodium citrate renders this blood unsafe after more than 5 days of refrigerated storage,[21] and this posed a serious obstacle to the widespread adoption of what is usually termed indirect transfusion. The permissible "dating period" of whole blood is considered to be the number of days of refrigerated storage at which a minimum of 70 percent of the infused red cells remain in circulation during the first 24 hours after transfusion.

Here again, this temporary check did not completely stop forward movement. The increasing use of blood led to further research in blood groups, and the discovery of the Rh factor [22] and subsequently of other subgroups increased the safety of transfusion. This progress has been continuous, until today our "panel" includes 20 or more proved antigens.

History affirms that technologic developments, in practically all fields, are of necessity stimulated during times of national danger, and great progress was made during World War II.[23] Figure 3 shows diagrammatically what we might term the *advance*, exploiting the *breakthrough*. Here we see the initial check of citrated blood (by the limitation of the 5-day dating period), overrun by a dual flanking movement. On the right, we see the development in whole blood. The addition of dextrose to citrated blood, by supplying substrate for the continuing metabolism of the red cell during storage, extended the useful period to 12 days, and blood so collected was extensively used in the early phases of the war. The addition of buffering citric acid [24] (ACD) prolonged the dating period to 21 days. This proved to be long enough for blood to be safely and effectively transported (under refrigeration) by air for thousands of miles. The overseas whole blood program of the Allies opened a new era in military medicine. Here we might refer to improvements in the *service of supply*.

The development of the closed vacuum bottle was a distinct improvement over open gravity collection. But the 21-day dating period, which is still a limitation, prevents the stockpiling of whole blood or red blood cells.

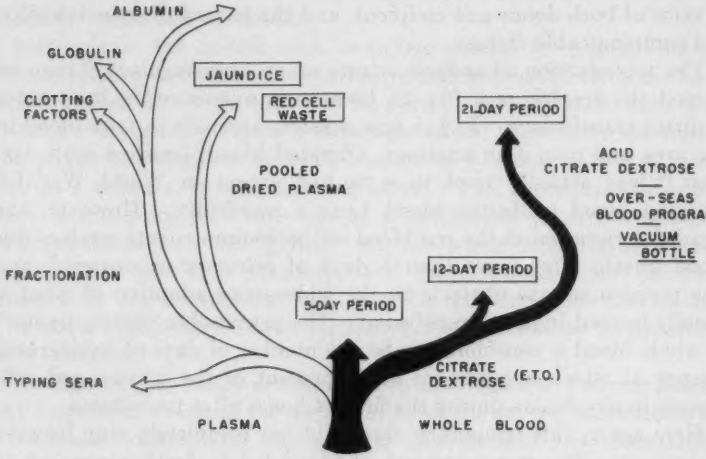


Figure 3. "The advance." Strong point—5-day dating period of citrated blood—overrun by dual flanking movement: advances in use of whole blood and red blood cells (*right*), and in plasma (*left*). (See text.) E.T.O.—European Theater of Operations.

Turning now to the flanking movement on the left, there had been extensive developmental work, before Pearl Harbor, in drying plasma from the frozen state, and lyophilized plasma was extensively used in World War II. Mass production by industry provided over 12 million units for the armed services or for stockpiling. This was the first large-scale use of a single blood component.[23]

There were distinct limitations in the use of plasma. It was not, and never can be, an adequate replacement for massive blood loss. In processing, the red cells were discarded, involving a tremendous waste of hemoglobin. In fact, the mass of hemoglobin discarded probably exceeded that of the total blood loss of all our combat casualties since Braddock's defeat. Dried plasma was found to transmit the virus of homologous serum jaundice, a comparatively rare disease before the war. Economical processing required pooling of plasma, and its use in thousands of cases established a reservoir of

infection. At the end of World War II this had become a serious problem.

Just prior to World War II, methods of fractionating plasma into the component proteins were developed under the lash of the onset of hostilities, and were rapidly perfected during World War II.[23] The fraction of principal military importance was serum albumin, which proved to be a most effective plasma volume expander. The fractionation process eliminated the hazard of virus transmission, and thus the serious obstacle of jaundice was bypassed. In addition, various globulins were found to retain very high titers of immune bodies. Other fractions had value as styptics, principally prothrombin and fibrinogen. As a supportive movement the development of typing serums with very high specificity increased the reliability of cross-matching technics and diminished the hazard of mismatching.

This, then, was the situation at the termination of World War II. Since then, continued efforts have resulted in further progress (fig. 4), which may be termed *mopping up*. Very little progress has been made in extending the dating period of whole blood. Citrate-phosphate-dextrose solution provides blood with a safe 30-day dating period, but must be regarded as still in the stage of clinical trial.[25] Extensive experimentation is currently being carried on to preserve red blood cells for prolonged periods at low temperatures (down to −80° C). If successful and practical, stockpiling of red cells may become a reality.

The advance on the whole blood front has taken 2 other directions. With open-heart surgery an established procedure, heparin has proved an effective anticoagulant for blood used to prime pump-oxygenators for extracorporeal circulation systems.

Ion exchange resins prevent coagulation of blood by completely removing calcium and magnesium ions.[26] "Soft" blood is of value in preventing citrate toxicity, as in hepatic disease, exchange transfusions in infants, and many other conditions.

Perhaps the most significant advance in this area has been made in the use of separated red cells. Clinical experience has shown that in about 30 percent of all hospital cases packed cells, when aseptically prepared, are much safer, in point of view of reactions and hemodynamic upsets, than whole blood. At this point, it might be in order to mention a further improvement in *service of supply*, namely, the development of safe and efficient plastic transfusion equipment.[27–28] With properly designed containers, the separation of red cells and plasma can be effected with no risk of bacterial contamination, and the separated cells may be returned to refrigerated storage and utilized for the full permissible dating period of whole blood,

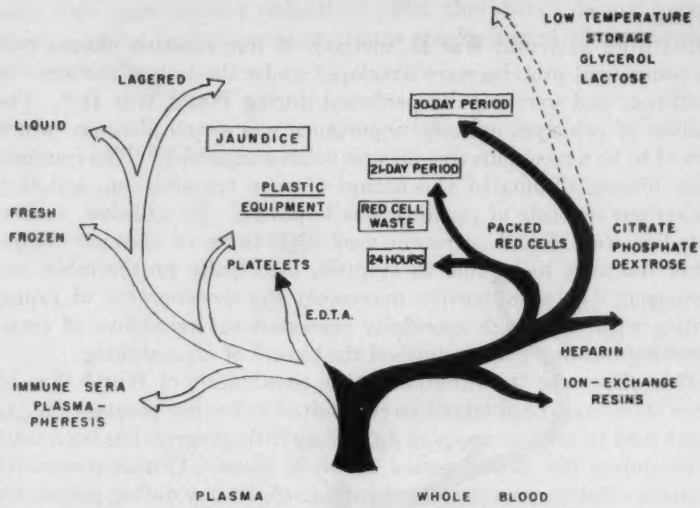


Figure 4. "Mopping up." (*Left*) Plasma stored at room temperature is effective as a plasma volume expander. Activity of many labile coagulation factors is well maintained in fresh-frozen plasma. Platelets, from fresh blood, are effective in stopping bleeding in thrombocytopenia. Plastic equipment permits aseptic separation of plasma and subsequent concentration of platelets in small volume. Edathamil (EDTA) is excellent anticoagulant for platelet blood. Further progress has been made in preparation of immune serums and labile clotting factors from plasma of blood collected through ion exchange resins. Plasmapheresis decreases safe interval between bleedings from months to weeks. (*Right*) Whole blood and red cells: Phosphate-buffered dextrose-citrate solution has increased the dating period of whole blood to 30 days. Heparin has proved an effective anticoagulant for extracorporeal circulation systems in open-heart surgery. Ion exchange resins prevent coagulation of blood by removing calcium and magnesium ions.

namely, 21 days.[29] Crosby and co-workers [30] recently demonstrated that plasma, in amounts sufficient to restore the hematocrit of ACD blood to precollection level (about 70 ml), can be removed without risk of contamination. The residual whole blood can be used for as long as 21 days, and the plasma can be used to augment the supply of the plasma bank, without additional cost.

Perhaps the most significant advance (fig. 4) is the finding that the storage of plasma at 80° F for 6 months (lagered plasma) renders the virus of homologous serum jaundice noninfective.[31-32] Plasma so stored is an effective plasma volume expander and its cost is far less

than that of serum albumin. Fresh-frozen plasma (−20° C) has been found to maintain labile factors such as antihemophilic globulin (AHG) for periods long enough to justify this procedure on a significant scale. These factors constitute a great incentive for the establishment of plasma banks in all hospitals. Such a program can be an outgrowth of the expanded use of separated red cells. Thus we see how the use of 2 apparently unrelated blood components can greatly increase the total effectiveness of a blood bank. It will be seen (fig. 4) that this advance was the result of a coordinated and successful *pincer* movement.

A most important advance resulting from methods for the aseptic separation of plasma from whole blood is the use of platelets in thrombocytopenia. The platelets must be harvested from fresh blood to assure maximum effectiveness. They may be administered as platelet-bearing plasma from lightly centrifuged blood, or concen-

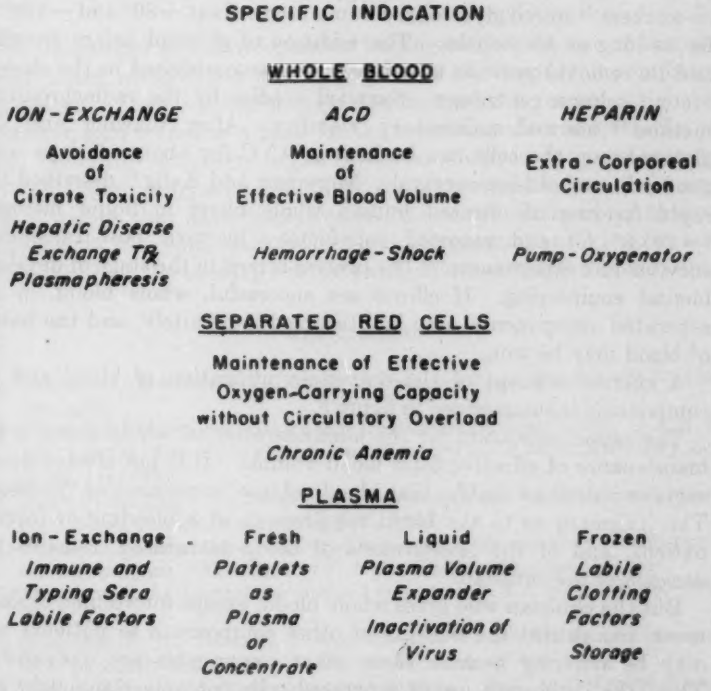


Figure 5. Specific indications for administration of blood and blood components. (See text.)

trated in a small volume by secondary centrifugation at a higher speed. Here again the use of plastic equipment offers a superior technic in terms of safety. Edathamil (EDTA, Versene) prevents coagulation by chelation of calcium and magnesium ion and has proved an excellent collection medium for blood intended for platelet harvest, especially when concentrates are required.

Further progress has been made in the preparation of immune serums from the plasma of blood from specifically sensitized donors.[33] Blood is collected through an ion-exchange column in a closed plastic system, permitting the immediate return of separated red cells to the donor (plasmapheresis), thus maintaining a normal red cell volume and decreasing the safe interval between bleedings from months to weeks.

In figure 4, the arrow at the upper right, in dotted outline, represents a continuing attack on the problem of stockpiling whole blood in the frozen state at temperatures as low as −200° C. Tullis and co-workers [34] stored glycerolized human red cells at −80° and −120° C for as long as 19 months. The addition of glycerol before freezing and its removal prior to transfusion was accomplished in the closed-system column centrifuge. Survival studies by the radiochromium method [35] showed satisfactory viability. After thawing and deglycerolizing, the cells can be kept at 4° C for about 10 days with good post-transfusion survival. Meryman and Kafig [36] described the rapid freezing of citrated human whole blood in liquid nitrogen (−195.8° C) and reported satisfactory in vivo post-transfusion survival in 2 experiments. The process is now in the stage of developmental engineering. If efforts are successful, whole blood, or its separated components may be preserved indefinitely, and the battle of blood may be won.

A current concept of the maximum utilization of blood and its components is summarized in figure 5.

The prime indication for the administration of whole blood is the maintenance of effective total blood volume. It is not always necessary, or indeed advisable, that blood volume be restored to "normal." The judgment as to the blood requirement of a bleeding or injured patient, and of the effectiveness of blood transfused, remains the decision of the clinician.

But the clinician who gives whole blood, except for volume replacement, has denied the benefits of other components to patients who may be suffering because these other components are unavailable. Thus, the large-scale use of separated cells not only completely and safely meets the requirements of 30 percent of patients with sub-

normal oxygen-carrying capacity but provides an ample supply of plasma for manifold uses: as a vehicle for platelets, labile factors, and immune bodies; as a plasma volume expander, involving no risk of transmission of virus disease; and as a limited source of nutrient.

Only when the proved components are kept in ready and ample supply can a blood bank be said to be functioning effectively. To achieve this effectiveness will require, primarily, that the medical profession acquire a fuller concept of the true value of blood components in therapy. This will take some time, since the principles involved are not taught with any clarity in most medical schools.

But we should already be thinking of the changes in the organization of our blood banks, the equipment for separation of components, the training of technicians in new technics, and the dispersal of storage depots, that will all become necessary when that time arrives.

SUMMARY

The discoveries and developments leading to the concept of therapy with blood components are portrayed as the record of a military campaign. Each successful operation met with a temporary check, but each gain served as a basis for the mounting of further attacks, so that the entire campaign, begun in the middle ages, has been marked by continuing progress. Diagrams are presented to show the many strong points that have been overrun, the coordination of the several movements in a combined attack, and the gradual encirclement and elimination of the obstacles to safe and effective blood transfusion.

REFERENCES

1. ELLIOTT, J.: Letter to J. F. Donnely. *Bull. Am. Assoc. Blood Banks* 12: 535, Dec. 1959.
2. FANTUS, B.: Therapy of Cook County Hospital; blood preservation. *J.A.M.A.* 109: 128–131, July 10, 1937; also Cook County's blood bank, *Mod. Hosp.* 50: 57–58, Jan. 1938.
3. JOINT BLOOD COUNCIL: *Directory of Blood Transfusion Facilities and Services*, Joint Blood Council, Washington, D.C., 1958.
4. GIBSON, J. G., 2ND: Use of separated human red cells; report of current practice and progress. *New England J. Med.* 250: 976–980, June 10, 1954.
5. JANEWAY, C. A.: Clinical use of blood derivatives. *J.A.M.A.* 138: 859–865, Nov. 20, 1948.
6. GARDNER, F. H., HOWELL, D. and HIRSCH, E. O.: Platelet transfusions utilizing plastic equipment. *J. Lab. & Clin. Med.* 43: 196–207, Feb. 1954.
7. GIBSON, J. G., 2ND: Blood component therapy. *Bull. South Central Assoc. Blood Banks* 2: 3–12, Dec. 1959.

562174 O—60——4

8. De Gowin, E. L., Hardin, R. C. and Alsever, J. B.: *Blood Transfusion*, W. B. Saunders Co., Philadelphia, Pa., 1949.
9. Strumia, M. M. and McGraw, J. J., Jr.: *Blood and Plasma Transfusions*, F. A. Davis Co., Philadelphia, Pa., 1949.
10. Mollison, P. L.: *Blood Transfusion in Clinical Medicine*, ed. 2, Blackwell Scientific Publications, Oxford, England, 1956.
11. Harvey, W.: *Exercitato Anatomica de Motu Cordis et Sanguinis in Animalibus* (Anatomical Studies on the Motion of the Heart and Blood). English translation with annotations by Chauncey D. Leake, centennial edition, Charles C Thomas, Publisher, Springfield, Ill., 1958, pp. 43–44, 74–75.
12. Landsteiner, K.: Über Agglutination—serscheinungen normalen menschlichen Blutes. *Wein. klin. Wchnschr.* 14: 1132, 1901.
13. Jansky, J.: Haematoloicke, studie u psychotiku. *Sborn. klin.* 8: 85, 1906–7.
14. Moss, W. L.: Studies on isoagglutinins and isohemolysins. *Bull. Johns Hopkins Hosp.* 21: 63, 1910.
15. Kimpton, A. R. and Brown, J. H.: New and simple method of transfusion. *J.A.M.A.* 61: 117, 1913.
16. Lindeman, E.: Simple syringe transfusion; new method applicable to infants and adults. *Am. J. Dis. Child.* 6: 28, 1913.
17. Unger, L. J.: New method of syringe transfusion. *J.A.M.A.* 64: 582–584, Feb. 13, 1915.
18. Lewisohn, R.: New and greatly simplified method of blood transfusion; preliminary report. *M. Rec.* 87: 141, 1915.
19. Rous, P. and Turner, J. R.: Preservation of living red blood cells in vitro. *J. Exper. Med.* 23: 219, Feb. 1916.
20. Robertson, O. H.: Transfusion with preserved red blood cells. *Brit. M. J.* 1: 691, June 22, 1918.
21. Gibson, J. G., 2nd, and others: Posttransfusion survival of preserved human erythrocytes stored as whole blood or in resuspension, after removal of plasma, by means of 2 isotopes of radioactive iron. *J. Clin. Invest.* 26: 715–738, July 1947.
22. Landsteiner, K. and Weiner, A. S.: Agglutinable factor in human blood recognized by immune sera for rhesus blood. *Proc. Soc. Exper. Biol. & Med.* 43: 233, Jan. 1940.
23. Baxter, J. P., 3d: *Scientists Against Time*, Little, Brown and Co., Boston, Mass., 1946, chap. 21, pp. 321–336.
24. Loutit, J. F., Mollison, P. L. and Young, I. M.: Citric acid–sodium citrate–glucose mixtures for blood storage; report to Medical Research Council from Southwest London Supply Depot. *Quart. J. Exper. Physiol.* 32: 183–202, Dec. 1943.
25. Gibson, J. G., 2nd, Rees, S. B., McManus, T. J. and Scheitlin, W. A.: Citrate-phosphate-dextrose solution for the preservation of human blood. *Am. J. Clin. Path.* 28: 569–578, Dec. 1957.
26. Walter, C. W.: New technic for collection, storage, and administration of unadulterated whole blood. *Surg. Forum* (1950), pp. 483–490, 1951.
27. Walter, C. W. and Murphy, W. P.: Closed gravity technique for preservation of whole blood in ACD solution utilizing plastic equipment. *Surg., Gynec. & Obst.* 94: 687–692, June 1952.
28. Walter, C. W., Button, L. N. and Ritts, R. E., Jr.: Evaluation of human blood processed in plastic transfusion equipment. *Surg., Gynec. & Obst.* 105: 365–369, Sept. 1957.

29. Gibson, J. G., 2nd, Pond, J. C. and McManus, T. J.: Viability of red cells of ACD blood asceptically separated from plasma in closed plastic system. Accepted for publication by *New England J. Med.*
30. Crosby, W. H., Williams, W. A. and Akeroyd, J. H.: Modification of standard plastic transfusion pack to permit collection of plasma. *U.S. Armed Forces M.J.* 11: 132–139, Feb. 1960.
31. Allen, J. G., Enerson, D. M., Barron, E. S. G. and Sykes, C.: Pooled plasma with little or no risk of homologous serum jaundice. *J.A.M.A.* 154: 103–107, Jan. 9, 1954.
32. Hoxworth, P. I. and Haesler, W. E., Jr.: Plasma transfusion without transmission of serum hepatitis. *J.A.M.A.* 166: 1291–1293, March 15, 1958.
33. Smolens, J., Stokes, J., Jr., McGee, E. and Hunter, V.: Feasibility and safety of frequent plasmapheresis of same human donors. *Proc. Soc. Exper. Biol. & Med.* 91: 611–614, April 1956.
34. Tullis, J. L. and others: Studies on in vivo survival of glycerolized and frozen human red blood cells. *J.A.M.A.* 168: 399–404, Sept. 27, 1958.
35. Gibson, J. G., 2nd, and Scheitlin, W. A.: Method employing radioactive chromium for assaying viability of human erythrocytes returned to circulation after refrigerated storage. *J. Lab. & Clin. Med.* 46: 679–688, Nov. 1955.
36. Meryman, H. T. and Kafig, E.: Rapid freezing and thawing of whole blood. *Proc. Soc. Exper. Biol. & Med.* 90: 587–589, Dec. 1955.

THE IDEAL PHYSICIAN

It is the possession of the scientific outlook that distinguishes the ideal physician from any well-veneered practitioner of the healing art. However, to study patients instead of diseases objectively requires of the observer a cultivated man capable of compassionate and perceptive responses. He must look at Nature for its own sake, as well as for the immediate value of the knowledge obtained. Fortunately, it is the actual training in observation that matures the observer emotionally at the same time as it develops intellect in the ways discussed above. Such a "trained observer" is more impartial in his judgments and more adequate to the task in general. Whether he becomes a research worker or a practitioner, he is rewarded by the thrill of discovery—similar to that described by the surgeon John Keats "on first looking into Chapman's Homer."—Raymond L. G. Newcombe: The Value of Observation in the Training of Medical Students. *The Medical Journal of Australia*, December 12, 1959.

Comparison of Chloramphenicol, Oxytetracycline, and Prochlorperazine in Salmonella Gastroenteritis

CAPTAIN JAMES E. MC GUIGAN, USAF, MC
COLONEL WILBUR C. BERRY, MC, USA
LIEUTENANT COLONEL PHILIP R. CARLQUIST, MSC, USA

THE ROLE OF CHLORAMPHENICOL (Chloromycetin) as a therapeutic agent for the treatment of typhoid fever has been well established,[1] and its use in this disease is generally considered mandatory. The picture is not nearly as clear concerning the role of antibiotics in the therapeutic approach to patients with the salmonelloses. There have been many conflicting reports [2-13] on the results of therapy with specific antimicrobial agents in patients afflicted with salmonella infections other than typhoid fever. To date there has been no report of a controlled study evaluating the efficacy of antibiotics in the treatment of salmonella gastroenteritis.

An outbreak of salmonella gastroenteritis observed by us provided an opportunity for evaluating results in a group of patients to whom antibiotics were administered as compared with a control group of patients who did not receive them. It is the purpose of this article to attempt to clarify the role of 2 antibiotics in the treatment of patients with gastroenteritis due to salmonella organisms other than *Salmonella typhosa*. This study concerns the therapeutic program and subsequent clinical course of a group of healthy young military personnel who were involved in an outbreak of salmonella gastroenteritis.

MATERIAL AND METHOD

In late August 1959, 26 enlisted personnel with a similar clinical picture were seen at the McChord Air Force Base Dispensary and hospitalized at this hospital. The most prominent symptoms were nausea,

From the Department of Medicine, Madigan General Hospital, Tacoma, Wash. Dr. Mc Guigan is now at 23101-84th St. West, Edmonds, Wash.

vomiting, abdominal cramping pain, diarrhea, and fever, all of varying severity. The group consisted of 25 men and 1 woman, all between 17 and 30 years of age.

Investigation revealed that all the involved patients had eaten a particular meal in one base dining facility and had reported to the dispensary with their complaints from 12 to 72 hours after eating. The meal consisted of turkey, turkey dressing, potatoes, peas, pudding, and milk or coffee. Investigation cf the dining hall revealed that thermometers on the ovens were broken, preventing exact knowledge of the temperature at which the large turkeys were cooked. Questioning of the food handlers revealed that the turkey had also been out of refrigeration and proper oven heat for 5 hours before being served.

Cultures for bacterial pathogens were obtained from all dining utensils and from all the foods eaten except the turkey, which unfortunately had been entirely consumed. These cultures all proved to be negative. Stool cultures of food handlers involved were also negative.

Stool cultures were obtained on all the hospitalized patients on either the day of admission or the day immediately following admission. In all 26 patients *Salmonella anatum* was recovered from the stool specimens. In no case was any other salmonella organism or any other gastrointestinal pathogen obtained.

The patients were then arbitrarily divided into 3 groups: group A, containing 9 patients, group B, containing 9 patients, and group C, containing 8 patients. All patients received supportive therapy, such as rehydration and antispasmodics, according to the severity of their clinical symptoms. In addition, the patients in group A received prochlorperazine (Compazine) dimaleate orally, 10 mg 4 times each day; those in group B received chloramphenicol orally, 250 mg 4 times each day; and those in group C received oxytetracycline (Terramycin) hydrochloride orally, 250 mg 4 times each day. The therapy was continued the 5 days during which the patients were hospitalized. At the end of this 5-day period the patients in all 3 groups were free of any gastrointestinal symptoms. The medications were discontinued at the time of discharge. Stool cultures were obtained on the day of discharge from all patients except patient 8 in group C.

RESULTS

The results of the cultures are shown in table 1. It is interesting to note that although all stool specimens were positive for *Salmonella anatum* on admission or shortly thereafter, there is a marked discrepancy among the different groups on the day of discharge. All

Table 1. ***Stool cultures for* Salmonella anatum *in 26 patients receiving prochlorperazine, chloramphenicol, or oxytetracycline***

Patients	*Day of admission*	*Day after admission*	*Day of discharge*	*Weeks following date of discharge from hospital*								
				2	*5*	*6*	*8*	*9*	*11*	*12*	*13*	*14*
GROUP A: PROCHLORPERAZINE												
1	+	+	+	+	+	0	−	−	−	−	−	−
2	0	+	+	−	0	0	0	−	0	−	0	−
3*	−	+	+	0	0	0	0	0	0	0	0	0
4*	+	0	+	0	0	0	0	0	0	0	0	0
5	+	+	+	0	+	0	−	−	0	0	0	0
6	+	+	+	+	−	−	−	0	−	−	−	−
7	+	0	+	+	−	0	+	−	−	−	−	−
8*	+	+	+	0	0	0	0	0	0	0	0	0
9	+	+	+	+	0	+	−	−	0	−	0	−
GROUP B: CHLORAMPHENICOL												
1	+	0	+	0	+	0	−	−	−	−	−	−
2	+	+	+	0	−	0	0	−	−	−	−	−
3*	+	−	−	+	0	0	0	0	0	0	0	0
4	0	+	+	0	+	0	0	−	0	−	−	0
5	+	0	+	+	−	0	−	−	0	−	−	−
6	+	0	+	+	+	0	+	−	0	−	−	−
7	+	+	−	+	+	0	−	−	−	−	0	−
8	+	−	+	−	−	0	+	+	−	−	−	0
9	+	+	−	0	−	0	0	0	0	0	−	0
GROUP C: OXYTETRACYCLINE												
1	+	+	−	−	−	0	0	0	−	0	−	0
2	+	+	−	0	−	0	−	−	−	−	−	−
3	−	−	−	+	−	0	−	+	−	0	0	0
4	+	−	−	0	−	−	−	−	0	−	−	0
5	+	−	−	+	+	+	0	0	0	−	0	0
6	+	−	−	0	+	+	+	+	0	−	0	0
7*	+	−	−	0	0	0	0	0	0	0	0	0
8	0	0	0	+	−	+	+	0	0	−	+	0

*Change of duty station following discharge from hospital.
+Stool specimen yielded *Salmonella anatum* on culture.
−Stool specimen negative for *Salmonella anatum* on culture.
0 No stool culture.

those who received prochlorperazine still had positive stools; those who received oxytetracycline all had negative stools; the patients who received chloramphenicol showed mixed results. Although the results of the stool cultures were markedly different in the 3 groups, there was no essential difference in the clinical pictures presented by patients in each group during hospitalization.

All patients were returned to duty after their 5-day hospitalization. Of the 26 patients 5 were transferred from McChord Air Force Base. Periodic stool cultures were obtained from the remaining 21 patients (table 1).

Two weeks following hospitalization results of stool cultures revealed that some of the patients who received oxytetracycline, who had previously been entirely negative, now had stools positive for *Salmonella anatum*. There was no appreciable difference among any of the 3 groups at the end of this 2-week period. The majority of patients in each group had positive stools. One patient in each group produced a stool negative for *Salmonella anatum* at that time.

Over the following 12 weeks all stool specimens reverted to negative except that of patient 8 in group C, who was readmitted to this hospital 13 weeks after discharge with gastroenteritis due to *Salmonella anatum*. Five weeks after the date of discharge there was no essential difference in the results of cultures on stool specimens submitted by the members of the 3 groups.

DISCUSSION

As previously noted, the use of chloramphenicol in the treatment of typhoid fever is universally recognized and accepted. By contrast, however, there is no body of evidence supporting the belief that this drug is of definite value in the treatment of salmonella gastroenteritis or other clinical entities caused by Salmonella species other than the typhoid bacillus. Neely and Nelson [13] administered chloramphenicol, 1 gram a day in divided doses for 3 days, to a small group of convalescent carriers of *Salmonella typhimurium*. There was no evident increase in the rate of clearance of the organisms from the stools as compared with untreated controls.

The clinical entities presented by patients with salmonellosis are classified by Saphra and Winter [14] and others [15, 16] as follows:

1. *Gastroenteritis*, varying in intensity from a benign picture to a full-blown exhaustive cholera-like disease. This group comprises from 65 to 70 percent of all salmonella infections observed clinically.

2. *Typhoidal and septic syndromes*, in which the patient may present a typhoid-like picture, with splenomegaly, rose spots, and a sustained fever, or the picture of septic infection, with a high spiking fever, leukocytosis, and a shift to the left. These represent 8 to 10 percent of the salmonella infections.

3. *Focal manifestations*, in which any organ may be involved with a localized infectious process, e.g., pneumonia, otitis media, cholecystitis, psoas abscess, empyema, or brain abscess. Into this category fall 7 to 8 percent of salmonelloses.

4. *Carrier states*, comprising 15 percent of salmonella infections, in half of which the patients have had previous clinical symptoms that may or may not have been diagnosed.

According to Meyer,[15] *Salmonella anatum*, the organism recovered in the present outbreak, is the fifth most common species of Salmonella isolated in the world. *Salmonella anatum* is found very frequently in poultry and poultry products. It is our impression

that although no turkey remained to be cultured, in this particular outbreak turkey was the most likely source of infection.

Investigators have estimated the fatality rate for salmonella infections as varying from 2.6 percent [16] to 5.3 percent.[11] Mortality occurs almost exclusively in young infants and in the elderly, particularly those with severe intercurrent disease. Eisenberg and co-workers [11] described a large series in which all 15 fatalities were patients suffering from severe associated disease states contributing in greater or less degree to the deaths of the patients.

In our group of healthy young adults suffering from the same infectious process, *Salmonella anatum* gastroenteritis, the administration of antibiotics did not appear to alter the clinical course of the disease. Nor did antibiotic therapy contribute to eliminating the pathogenic agent from the stools, since those who had not received specific antimicrobials also submitted negative stools.

The occasional severe complications of antibiotic therapy such as mycotic overgrowth and staphylococcic pseudomembranous colitis are well known. In view of their apparent lack of effectiveness in altering the course of *Salmonella anatum* gastroenteritis, it appears that the use of these agents is both injudicious and contraindicated in this disease. Because of their possible side effects Saphra [17] also advocates restraint in the use of antibiotics in certain salmonelloses.

SUMMARY AND CONCLUSIONS

An outbreak of gastroenteritis due to *Salmonella anatum* involving 26 military personnel is described. No other stool pathogen, salmonella or otherwise, was obtained. The patients were treated with either chloramphenicol, oxytetracycline, or prochlorperazine; all recovered clinically within a 5-day period. There was no difference in the clinical symptoms between those who did and those who did not receive antibiotics; and no difference in the results of the stool cultures for *Salmonella anatum* following hospitalization between those who did and those who did not receive antibiotics. Morbidity in this group of healthy young military personnel was not great.

Salmonella gastroenteritis is a benign disease in a healthy young adult population. Neither the clinical course nor the results of the immediate convalescent stool cultures are materially affected by the administration of antibiotics.

Because of the occasional severe complications of therapy with antibiotics and their ineffectiveness in modifying *Salmonella anatum* gastroenteritis, their use is felt to be injudicious and contraindicated in this condition.

REFERENCES

1. Woodward, T. E., Smadel, J. E. and Ley, H. L., Jr.: Chloramphenicol and other antibiotics in treatment of typhoid fever and typhoid carriers. *J. Clin. Invest.* 29: 87–99, Jan. 1950.
2. Zimmerman, L. E.: Treatment of salmonella infections with chloramphenicol and Terramycin. *U.S. Armed Forces M. J.* 3: 503–514, April 1952.
3. Scott, R. B. and Wooding, C. H., Jr.: Terramycin hydrochloride in treatment of Salmonella choleraesuis bacteremia. *Pediatrics* 7: 349–354, March 1951.
4. Streitfeld, M. M., Saslaw, M. S. and Lawson, R. B.: Chloramphenicol-tetracyline treatment of salmonellosis in children; strip-gradient and replica strip-gradient techniques as guides to therapy. *A.M.A. J. Dis. Child.* 94: 155–168, Aug. 1957.
5. Doran, J. H.: Salmonellosis: 9 cases successfully treated with Chloromycetin. *Ann. Int. Med.* 37: 714–722, Oct. 1952.
6. Weiner, H. A. and Liebler, J. B.: Infections with multiple salmonella types, including S. Braenderup; results of chloramphenicol treatment. *J.A.M.A.* 145: 802–806, March 17, 1951.
7. LaCore, I. A. and Conlin, J. H.: Use of Chloromycetin in treatment of salmonella carriers in state institution. *Am. J. M. Sc.* 225: 547–550, May 1953.
8. Rabe, E. F.: Treatment of salmonellosis with massive doses of penicillin compared with other methods of therapy. *Pediatrics* 16: 590–598, Nov. 1955.
9. Kunstadter, R. H., Milzer, A. and Kagan, B. M.: Chloramphenicol and Terramycin in treatment of salmonella and shigella infections. *J. Pediat.* 39: 687–697, Dec. 1951.
10. Ross, S., Burke, F. G., Rice, E. C., Washington, J. A. and Stevens, S.: Chloromycetin in treatment of salmonella enteritis. *New England J. Med.* 242: 173–176, Feb. 2, 1950.
11. Eisenberg, G. M., Brodsky, L., Weiss, W. and Flippin, H. F.: Clinical and microbiological aspects of salmonellosis; study of 95 cases in adults and children. *Am. J. M. Sc.* 235: 497–509, May 1958.
12. Cheever, F. S.: Acute diarrheal diseases of bacterial origin. *Bull. New York Acad. Med.* 31: 611–626, Sept. 1955.
13. Neely, R. A. and Nelson, M. G.: Salmonella food poisoning due to duck eggs with trial of chloramphenicol on carrier state. *Month. Bull. Min. Health* 10: 96–101, April 1951.
14. Saphra, I. and Winter, J. W.: Clinical manifestations of salmonellosis in man; an evaluation of 7779 human infections identified at New York Salmonella Center. *New England J. Med.* 256: 1128–1134, June 13, 1957.
15. Meyer, K. F.: Medical progress: Food poisoning. *New England J. Med.* 249: 804–812, Nov. 12, 1953.
16. Rubenstein, A. D., Feemster, R. F. and Smith, H. M.: Salmonellosis as public health problem in wartime. *Am. J. Pub. Health* 34: 841–853, Aug. 1944.
17. Saphra, I.: Antibiotic treatment of enteral or parenteral Salmonella infections. *Antibiotic Med.* 3: 437–438, Dec. 1956.

Polyneuritis: Clinical Review of 23 Cases of Landry-Guillain-Barré Syndrome

CAPTAIN ROGER C. DUVOISIN, USAF, MC

IN CONTEMPORARY USAGE the term polyneuritis refers to the distinctive picture of a bilateral, symmetric, mainly distal weakness of the extremities, accompanied by a depression of the tendon stretch reflexes in the affected limbs. To this may be added paresthesias, and a symmetric distal sensory deficit usually confined to an impaired appreciation of vibration, position, and touch. The symmetric pattern is in contrast to the irregular patchy distribution of neuropathy, indicated by the term mononeuritis multiplex, that is characteristic of periarteritis nodosa.

Despite a diversity of known causes and extreme variations in its chronology, the clinical picture is so remarkably constant that polyneuritis may justifiably be considered a clinical entity. The etiologic agent in a given case may be suggested by the setting in which the disease is encountered or by associated features when the neuropathy is a manifestation of a disease of metabolism, malnutrition, specific vitamin deficiency, chemical intoxication, or certain infections such as diphtheria and infectious mononucleosis. Such an origin may at times be revealed only by specific laboratory examinations. In some cases the relationship of polyneuritis to a pre-existing disease such as carcinoma, diabetes mellitus, sarcoidosis, or lupus erythematosus remains speculative, even though this distinctive neuropathy has been considered a direct expression of these and other disorders. In the great majority of cases encountered in clinical practice no cause can be found.

A large proportion of these idiopathic cases of polyneuritis are seen in healthy young adults, who may rapidly develop a severe generalized

---

From the Neurology Service, USAF Hospital, Lackland Air Force Base, Texas. Presented 5 February 1960 at the Third Annual Meeting of the Society of Air Force Internists and Allied Specialists at this hospital.

paralysis and make a remarkable recovery. They form a distinctive group, recognized as an entity a century ago by Landry,[1] who described 10 cases illustrating the various clinical presentations known today under a number of diagnostic terms, including "infectious polyneuritis," "polyneuritis with facial diplegia," "infectious neuronitis," "acute polyneuritis of unknown cause," and "Guillain-Barré syndrome." Landry noted that weakness usually appeared first in the distal portions of the extremities and ascended to involve the face and then the trunk; symptoms in a few cases began in the upper limbs first, and in others were generalized from the onset of the illness. Landry's name, however, later became associated with the concept of an ascending sequence of paralysis, which has been fancifully visualized as climbing the spinal cord segment by segment as a ladder.[2]

Numerous case reports and reviews over the past century have established the principal clinical features of polyneuritis, and several merit particular reference because of their historical significance. Leyden [3] described the clinical differentiation of Landry's paralysis from poliomyelitis. This is a point of interest because in recent years the term Landry's paralysis has been applied to cases of poliomyelitis displaying a very acute severe generalized paralysis. Ross [4] reviewed the literature, collected 93 cases, and concluded that Landry's paralysis was a peripheral neuritis. Osler,[5] and later Gordon Holmes,[6] described the disease as "acute febrile polyneuritis." The terms "acute infectious polyneuritis" and "infectious neuronitis" reflected the widespread belief that an infectious agent, probably viral, was the cause.

Guillain, Barré and Ströhl [7] reported 2 cases in a brief article in which they stressed 2 features: an "acellular hyperalbuminosis" of the spinal fluid, and delayed as well as diminished myotatic reflexes demonstrable on mechanical myographic recordings. The spinal fluid formula attracted an enormous amount of attention. Over the subsequent 20 years Guillain developed his thesis that a small number of cases having a favorable prognosis could be distinguished from that "vast motley of common polyneuritides" [8] by the albuminocytologic dissociation. Guillain stated that in cases of his syndrome the spinal fluid protein usually amounts to 1 to 2 grams per 100 ml, and that "cases with slight hyperalbuminosis with an albuminoid content of from 0.3 to 0.4 grams do not belong to the syndrome or must be regarded as instances of an abortive form."

Common usage has sanctioned the inclusion, under the eponym "Guillain-Barré syndrome," of cases that have a much less marked elevation of the spinal fluid protein. Thus Guillain's emphasis on the

favorable prognosis in his syndrome has been extended to that "vast motley" with the consequence that polyneuritis is generally regarded as a more benign disease than it actually is. However, the significance of the albuminocytologic dissociation has been challenged frequently, and serious clinicians have been unable to confirm the prognostic value of the spinal fluid findings.[9] Cases with extreme elevation of the spinal fluid protein may end fatally and, conversely, typical cases may fail to develop the albuminocytologic dissociation. Forster, Brown and Merritt,[10] for example, found that the protein was within normal values in 7 of 26 cases of polyneuritis with facial diplegia. Furthermore, even a marked pleocytosis may occur.

With the development of adequate methods of caring for respiratory paralysis, it has become widely appreciated that this is the main cause of death in polyneuritis, and that if ventilation can be successfully maintained even the most severe cases can recover.[11] Thus, Guillain's argument that cases ending fatally do not belong to his syndrome cannot be accepted.

Since Landry's cases otherwise meet Guillain's well defined clinical criteria, it has been suggested that the familiar eponym be enlarged to include Landry's name, i.e., "Landry-Guillain-Barré syndrome." [12] This newer designation has achieved general acceptance, corrects the tendency prevalent in recent years to separate the acute "ascending" cases, and properly de-emphasizes the spinal fluid formula identified with the older term "Guillain-Barré."

CLINICAL ASPECTS

Recent experiences at this hospital led to a review of the 23 cases of polyneuritis that had been encountered in the preceding 3-year period. A brief clinical analysis of these cases, 10 of which were observed personally, is presented, with special emphasis on the spinal fluid examination, the final outcome, and the most common diagnostic errors. Cases of polyneuritis that were due to acute intermittent porphyria, diabetes mellitus, or heavy metal intoxication were omitted. However, following the precedent of Haymaker and Kernohan,[12] 2 cases having diagnostic serum titers of heterophil agglutinins were included.

Our patients ranged in age from 3 to 36 years; 17 were between 17 and 25 years of age (table 1). All but 2 were males. This age and sex incidence reflects the fact that our patients were drawn from a military population.

Preceding infections, all relatively minor upper respiratory infections, had occurred in 14 patients. Two patients had had preceding

Table 1. *Summary of clinical data*

Case	Age and sex	Maximal neurologic deficit		Initial CSF protein (mg/100 ml)	Time of recovery, return to duty, or separation (months)	Residual deficit*	Disposition
		Grade*	Time attained				
1	21M	VII	3d week	190	4	O	Duty
2	19M	VI	3d week	97	7	I	Separated
3	17M	V	2d week	118	6	II	Separated
4	19M	VII	4th day	78	12	IV	Separated
5	32M	II	2d week	112	4	O	Duty
6	21M	IV	3d day	112	3½	O	Duty
7	23M	VI	6th day	68	24	IV	Separated
8	21M	II	2d week	62	2	**O	Duty
9	36M	VII	3d week	42	9	O	Duty
10	18M	VI	3d day	24	6½	***IV	Separated
11	20M	V	2d week	192	7	O	Duty
12	34F	V	4th week	24	7	O	-
13	34M	VI	4th week	92	14	***IV	Separated
14	19M	VI	2d week	144	6	III	Separated
15	17M	IV	6th day	32	3	I	Duty
16	20M	III	2d month	156	6	O	Duty
17	20M	VII	6th day	89	9	O	Duty
18	19M	IV	2d month	250	12	O	Duty
19	20M	IV	3d week	24	7	I	Separated
20	21M	VII	4th day	30	9	I	Separated
21	3F	V	3d week	181.5	1½	O	-
22	20M	III	2d week	156	4	O	Duty
23	28M	IV	6th month	190	17	IV	Separated

*Grades of neurologic deficit:

Grade	Weakness	Gait impairment	Impairment of respiration
I	Subjective	None	None
II	Minimal	Minimal	None
III	Moderate	Slight foot drop	None
IV	Marked	Moderate; short braces	None
V	More marked	Marked; walking only with assistance or long leg braces	None
VI	Severe	Bedridden	Dyspnea
VII	Maximal	Bedridden	In respirator

**Residual facial weakness.

***Follow-up examinations showed no further recovery 2 years after onset of polyneuritis.

trauma in the form of a dental extraction in one, and in the other an assault resulting in a fractured jaw and cerebral concussion. The possible causal relationship between preceding infection or trauma and polyneuritis has been noted frequently but remains a speculative matter that deserves further study.

The acuteness of the illness can be evaluated by observing the length of time between onset and development of the maximal neurologic deficit. The deficit appeared to have attained its peak within the first week in 7 patients, the second in 6, the third in 5, and the fourth in 2. Three patients pursued a more chronic course; 2 experienced the greatest disability in 2 months and 1 in 6 months.

Paresthesias were reported by all who were interrogated on this point specifically. In addition, 8 patients complained of aching lumbar pain at the onset of the illness. Several complained also of crampy pains in the legs. Muscle tenderness was noted in all patients in whom the affected muscles were palpated. Only 8 patients were febrile during the acute phase of the illness, but none had a rectal temperature above 102° F.

Weakness appeared first in the lower extremities in 14 patients, in the upper extremities in 2, and in the facial musculature in 2, but was generalized in 5 cases. Although proximal limb and girdle weakness was prominent in several patients with moderately severe neurologic deficit, weakness was always greater in the distal portions of the affected limbs. The lower limbs were affected in all 23 patients but paralysis was confined to the legs in only 3. One patient had marked facial diplegia and minimal weakness in the lower extremities. In general, when weakness in the lower extremities was marked, the upper limbs showed some weakness, but there was wide individual variation. Marked distal atrophy was observed in 2 severely paralyzed patients, but recovery was nearly complete.

Cranial nerve paresis was noted in 13 patients. Multiple cranial nerve involvement was the rule. In only 3 patients was a single nerve involved and these patients had facial diplegia. Facial weakness was observed in 8 patients and paresis of the pharyngeal muscles in 7. It is likely that a mild facial diplegia may have been overlooked in some cases.

An objective sensory deficit was found in only 7 patients and was limited to diminished appreciation of vibration, position, and touch and impairment of 2-point discrimination. Loss of 2-point discrimination was not found without concomitant impairment of light touch, but was a more objective measure of sensory deficit. Vibratory sensation was the earliest modality affected and in 1 patient it was the only modality impaired. Loss of sensation was confined to the distal portions of the affected limbs and was never present without some corresponding muscle weakness. However, the severity of paralysis was not proportionate to the degree of sensory deficit. Thus, 1 patient was almost totally paralyzed on the fourth day of

illness, but at no time was it possible to find any impairment of sensation.

Depression or disappearance of the tendon stretch reflexes was observed in every patient and was helpful in establishing the clinical diagnosis. The relative time of appearance of hyporeflexia and the degree of persisting reflex activity varied. In 1 moderately severe case in which the patient was able to ambulate only with assistance, the knee and ankle jerks could be elicited without reinforcement, but were unobtainable during convalescence and still absent after full recovery. In contrast, in a patient in whom facial diplegia was the first manifestation of polyneuritis, the knee and ankle jerks became unobtainable approximately 1 week before objective weakness could be demonstrated and had not returned 1 year after full clinical recovery. The maximal deficit in this case consisted of minimal distal weakness of the lower extremities.

In 5 patients respiratory muscle paralysis was sufficient to require the use of an artificial respirator, and all were managed with tank-type respirators. In addition, a chest respirator was used during the early recovery phase for 1 patient, and rocking beds, in a later recovery phase, for 3. Tracheotomy was performed in all 5 patients; and they were placed in the respirator on the second, fourth, sixth, fourteenth, and seventeenth day of illness, respectively. Constant artificial ventilation was required for periods varying from 4 days in the most benign to 2 months in the most severe case. In 3 patients recovery was complete; the other 2 were separated from military service with generalized weakness, although both were fully ambulatory.

All 5 respirator patients developed pneumonia. Two pursued a particularly stormy course, with episodes of atelectasis requiring repeated bronchoscopy for aspiration of mucous plugs. The deflator was found to be of some value in these patients. Cultures of tracheal and bronchial material grew *Diplococcus pneumoniae* in 2 cases, *Staphylococcus aureus* in 2, and pseudomonas organisms in 1. Improvement of pulmonary infections paralleled recovery from paralysis. Decubitus ulcers developed in the 3 patients who required more prolonged use of the respirator.

It was thought initially that 4 of the respirator patients had hysterical paralyses; consequently, there may have been some delay before a tracheotomy was performed and proper respirator care instituted. Although all respirator patients enjoyed a favorable outcome, it seems pertinent to point out the danger of mistaking a fulminating case of the Landry-Guillain-Barré syndrome for hysteria. It is believed that

the well-established criteria for management of respiratory weakness used for poliomyelitis should be applied with additional caution in cases of acute polyneuritis. The course of the disease may be more erratic and the earlier appearance of pharyngeal muscle weakness renders the likelihood of aspiration greater than in acute poliomyelitis.

The rate and extent of recovery were closely related neither to the severity of the disease nor to the acuteness of the onset except that in no instance of chronic onset was recovery rapid. One patient reached the maximal neurologic deficit on the sixth day of the illness, but recovery extended over a 2-year period. The most rapid recovery occurred in 6 weeks. Only 8 patients (cases 1, 5, 6, 8, 15, 16, 21, 22) could be considered to have made a reasonably complete recovery within 6 months. One of these, however, had residual facial weakness; and one had subjective weakness and increased fatigability on resuming duty 2 and 3 months respectively after the onset of the illness. One patient (case 10) had attained his maximal recovery in the sixth month of his illness and was unchanged at the end of 2 years. Of the 23 patients, 11 made a full recovery during the period of observation. Two cases (8, 15) returned to duty with minimal residua. The most chronic patient (case 23) reached his maximal deficit in the sixth month of illness and was very slightly improved when last examined in the seventeenth month; at this time he had marked distal lower extremity weakness requiring short leg braces. Another patient (case 4) had marked generalized weakness but could ambulate well with short leg braces at the end of 1 year. Three patients (cases 7, 10, 13) were considered to have reached a plateau of recovery in 2 years, at which time they could ambulate with braces. The remaining 5 patients were separated from military service with significant minimal to moderate lower extremity weakness, 2 in the sixth, 2 in the seventh, and 1 in the ninth month of illness; the ultimate outcome of these patients is not known.

Some patients were returned to duty before complete recovery with minor residual weakness or abnormal fatigability. The 11 recovered military patients were returned to duty after hospitalization or convalescent leave for an aggregate total of 61 months. Ten military cases were terminated by separation for residual disability after an aggregate total hospitalization and convalescent leave of 101 months. At the time of separation, 3 were ambulatory with short leg braces, 2 required long braces, 1 had moderate lower extremity weakness, 1 had minimal lower limb weakness, and 3 had no objective neurologic deficits but complained of leg weakness and were incapacitated for military duty by abnormal fatigability. It is believed that an illness

producing this much morbidity and disability should be regarded with appropriate respect and should not be dismissed as a benign entity.

SPINAL FLUID STUDIES

Lumbar punctures were performed on all patients (table 2). The protein value on initial puncture was less than 45 mg per 100 ml in 6 patients, between 100 and 200 mg per 100 ml in 10, and over 200 mg per 100 ml in only 1 patient. Of the 11 patients in whom spinal fluid was obtained during the first week of illness, 5 had a protein less than 45 mg per 100 ml. By contrast, of the 15 patients in whom the protein was measured during the second, third, or fourth week of the illness, only 2 had a value below 45 mg per 100 ml. The highest value observed was 634 mg per 100 ml in the ninth month of illness in the most chronic case. Of the 5 patients who had normal protein in the first week of illness, 4 had subsequent elevations to 84, 130, 150, and 270 mg per 100 ml, respectively. There was thus a distinct tendency for the spinal fluid proteins to rise during the course of the illness, but no correlation existed between the protein content of the fluid and the severity of the illness.

Table 2. ***Protein content of spinal fluid in 23 patients***

Protein content (mg/100 ml)	*Number of patients*	
	Initial puncture	*Highest value*
Less than 45	6	2
45 to 75	2	0
75 to 100	4	3
100 to 200	10	11
200 and over	1	7

Pleocytosis was found in 6 patients; in all of these the increase in cellular elements consisted of a lymphocytosis ranging from 12 to 253 lymphocytes per cu mm. In no case was there a rise in polymorphonuclear cells or xanthochromia. Colloidal gold curves were obtained in 14 patients, in 9 of whom there was a midzone ("tabetic") curve, in 1 a first-zone ("paretic") curve, and in 1 a reaction in the higher dilutions ("meningitic curve"). In 4 patients the curve was flat, despite an elevation of the protein in 3 of these. An abnormal colloidal gold test was in every instance associated with an elevated spinal fluid protein.

562174 O—60——5

The significance of these abnormalities of the cerebrospinal fluid is not entirely clear. Since the principal site of pathologic change is in the spinal roots, a concomitant alteration of the blood-spinal fluid barrier may occur, with a resultant rise in spinal fluid protein. Modern work on the formation of cerebrospinal fluid has shown that the fluid is formed throughout the neuraxis and that a dynamic exchange of proteins and electrolytes occurs in the spinal subarachnoid spaces.[13] Thus any radiculopathy may be expected to produce alterations in spinal fluid proteins.

In the Landry-Guillain-Barré Syndrome the severity of pathologic alterations is proportional to the duration of the disease rather than to the severity of the neurologic deficit.[12] Patients dying within the first week present no changes. The earliest changes consist of interstitial edema and vascular engorgement. These may be followed by swelling and later degeneration of the myelin sheaths accompanied by the appearance of histiocytes, Schwann cell proliferation, and lymphocytic infiltration. Inflammatory changes appear to be secondary and are only rarely pronounced.

This pathologic picture would thus seem to be compatible with the spinal fluid alterations observed in this and other series of cases. The albuminocytologic dissociation may reflect merely an alteration of the blood-spinal fluid barrier consequent upon a primarily degenerative radiculopathy. The infrequent occurrence of pleocytosis corresponds to the paucity of inflammatory cells at the site of the lesion. The delay in the appearance of pathologic alterations is paralleled by a similar delay in the development of an elevation of spinal fluid protein.

The gross disparity that may exist between anatomic evidence of altered structure and clinical evidence of disturbed function is well exemplified in polyneuritis. There is no a priori reason why alterations in the blood-spinal fluid barrier must accurately reflect changes in the function of axons passing through the affected roots even if such alterations could be correlated with observed pathologic change. It may be concluded from these considerations and from clinical observations that the spinal fluid protein content has no prognostic, and little diagnostic, value in individual cases.

PROBLEMS OF DIFFERENTIAL DIAGNOSIS

The most common erroneous diagnosis—hysteria—entertained in this series, was considered seriously in 6 patients, all of them very ill, with 4 requiring respirator care. The tendency to regard the more acute cases of polyneuritis as functional has received previous comment in

the literature.[14] The patient presents himself with a severe generalized paralysis but has no fever and may not appear truly ill. He may seem anxious and apprehensive, especially if there is weakness of the muscles of respiration. An element of ataxia may lend a bizarre appearance to the movements of paretic limbs. Pelvic girdle weakness may result in inability to arise unassisted but permit a fair degree of ambulation, although with a waddling, unsteady gait. These apparent inconsistencies may mislead the examining physician and confirm his suspicion that the patient has "functional" disease.

Since patients with the most acute disease are also the most likely to have a normal spinal fluid protein, the danger of relying too much on this laboratory finding needs particular emphasis. Even in cases in which the diagnosis is established, a functional element may often be suspected and the patient submitted prematurely to an active program of physical therapy that may result in injury to articular structures. One convalescent patient, in the present series, suffered recurrent synovial effusions in one knee that probably represented traumatic injury to a joint inadequately protected by its paretic musculature.

Poliomyelitis was the leading diagnostic impression in 4 acute cases. This may be a proper differential diagnosis that should certainly be considered carefully in some cases. Excessive reliance on the spinal fluid findings delayed the correct diagnosis in these 4, otherwise characteristic, cases of polyneuritis because the patients failed to develop the albuminocytologic dissociation. Attention to clinical features such as the pattern of muscle weakness, the absence of fever, the manner of progression of neurologic deficit, and the symmetric depression of reflexes should rarely fail to distinguish cases of polyneuritis from poliomyelitis, whether or not they have the proper spinal fluid formula or sensory findings.

In 3 patients pursuing a chronic course the diagnosis of muscular dystrophy was entertained. Other authors have noted a similar experience in children with polyneuritis.[15] The pelvic girdle musculature may be involved sufficiently to produce a waddling gait, straddling stance, and Gower's sign, and thus the proximal limb–girdle pattern of weakness so characteristic of the muscular dystrophies may be mimicked.

In one patient, a child 3 years old, an unsteady, broad-based gait led to a suspicion of a posterior fossa tumor. In another patient, roentgenograms of the feet obtained because of the complaint of tingling and numbness revealed "march fractures." Progressive weakness and areflexia while under orthopedic observation led subsequently to the correct diagnosis. Unilateral facial paralysis in one patient was

thought to be Bell's palsy, but when bilateral facial paresis was noted and the patient subsequently developed minimal weakness of the lower extremities and loss of the stretch reflexes, the correct diagnosis became apparent.

A correct initial diagnosis was made in only 7 cases. Although in the remainder it was often considered in the differential diagnosis, it was withheld most frequently because the spinal fluid findings were not considered typical. However, the only patient whose spinal fluid met Guillain's criteria presented a very slowly progressive course and was suspected of having a spinal cord tumor. Thus it is pertinent to make a plea for greater consideration of the purely clinical features—that is, the history and a proper physical examination—and less interest in the spinal fluid formula in cases in which the diagnosis of the Landry-Guillain-Barré syndrome is under consideration.

The 2 patients with diagnostic titers of heterophil agglutinins were in no other way distinguishable. Heterophil agglutinins were measured in 7 patients; and it is certainly possible that more cases would have been recognized had the proper laboratory tests been requested routinely. Both acute and convalescent phase sera should be studied for evidence of a rising titer.

The urine test for porphobilinogen was performed in 9 patients with negative results. During the 3-year period under study, 6 cases of acute intermittent porphyria were encountered. In 2 of these patients a typical acute polyneuritis, sufficiently severe to require respirator care, developed. A psychotic reaction in one and abdominal pains in the other suggested the diagnosis. However, it is worthy of note that in 1 of these patients the urine was examined almost daily for porphobilinogen and not until the eighteenth sample was a positive test encountered. Thus the urine should be tested repeatedly during the course of the illness, and the possibility of this diagnosis must be constantly kept in mind.

THERAPY

Five patients were treated with steroid drugs for periods of time ranging from 2 to 6 weeks; and 2 received corticotropin (ACTH) injections during the acute phase of the illness. No beneficial effect was observed. One patient received BAL (dimercaprol) injections for several days without effect. General supportive measures and nursing care formed the basis of the medical management. Physiotherapy was an important therapeutic element during the acute, as well as the convalescent phase of the illness, if only because morale was main-

tained thereby. Rehabilitation measures were necessary in patients with significant residual neurologic deficit.

It is apparent that no effective therapy is available for polyneuritis. Rare patients responsive to steroid medication and one demonstrating steroid dependence have been described.[16] However, similar bouts of polyneuritis have developed in patients with Cushing's syndrome [17] and in patients already on maintenance steroid therapy for other conditions, for example, rheumatoid arthritis.[18] Thus the use of steroid agents remains of uncertain value. It is hoped that work in progress on experimental allergic polyneuritis may lead to newer therapeutic approaches.

SUMMARY

A brief historical review of the Landry-Guillain-Barré syndrome and a clinical analysis of 23 cases are presented. It is concluded that the albuminocytologic dissociation commonly encountered in this condition has no prognostic significance and may be frequently lacking in otherwise indistinguishable cases, especially in the first week of the disease. There should be greater reliance on the clinical picture as a whole. Thus diagnosis should not depend on the spinal fluid findings.

In 10 patients in the present series, recovery was not sufficiently complete to permit retention in military service. Five patients had severe residual deficit 1 year after the onset of the illness. It is suggested that there is a significant incidence of persistent residual deficit in this illness and that the general impression of benignity associated with the eponym "Guillain-Barré" should be corrected. Attention is directed to the prolonged period of hospitalization and convalescence required even in patients making a full recovery.

The erroneous diagnoses are analyzed; the most frequent were hysteria, poliomyelitis, and muscular dystrophy.

REFERENCES

1. Landry, O.: Notê sur la paralysie ascendante aiguë: *Gaz. hebd. med. chir.* 6: 472–474, July, and 486–488, Aug. 1859.
2. Fay, T., in discussion on Thorner, M. W., Alpers, B. J. and Yaskin, J. C.: Acute ascending paralysis (Landry's paralysis): clinicopathologic study. *Arch. Neurol. & Psychiat.* 44: 17–42, July 1940.
3. Leyden, E.: Über Poliomyelitis und Neuritis. *Ztschr. f. klin. Med.* 1: 387–434, 1880.
4. Ross, J.: On peripheral neuritis. *Med. Chronical* 10: 356–357, Aug. 1889.
5. Osler, W.: *The Principles and Practice of Medicine*, ed. 1, D. Appleton & Co., New York, N.Y., 1892, pp. 777–778, and 835–836.

6. HOLMES, G.: Acute febrile polyneuritis. *Brit. M. J.* 2: 37, July 14, 1917.
7. GUILLAIN, G., BARRÉ, J. A. and STRÖHL, A.: Sur un syndrome de radiculonevrite avec hyperalbuminose du liquide céphalo-rachidien sans réaction cellulaire; remarques sur les caractères cliniques et graphiques des réflexes tendineux. *Bull. et mém. Soc. med. hôp. Paris.* 40: 1462–1470, Oct. 13, 1916.
8. GUILLAIN, G.: Radiculoneuritis with acellular hyperalbuminosis of the cerebrospinal fluid. *Arch. Neurol. & Psychiat.* 36: 975–990, Nov. 1936.
9. DE JONG, R. N.: The Guillain-Barré syndrome; polyradiculoneuritis with albuminocytologic dissociation. *Arch. Neurol. & Psychiat.* 44: 1044–1068, Nov. 1940.
10. FORSTER, F. M., BROWN, M. and MERRITT, H. H.: Polyneuritis with facial diplegia; clinical study. *New England J. Med.* 225: 51–56, July 10, 1941.
11. DREIFUSS, F. E., HURWITZ, L. J. and JOHN, C.: Polyneuritis requiring artificial respiration. *Lancet* 2: 59–63, July 1957.
12. HAYMAKER, W. and KERNOHAN, J. W.: The Landry-Guillain-Barré syndrome; clinicopathologic report of 50 fatal cases and critique of literature. *Medicine* 28: 59–141, Feb. 1949.
13. WOLSTENHOLME, G. E. W. and O'CONNOR, C. M.: *The Cerebrospinal Fluid, Production, Circulation and Absorption.* A Ciba Foundation Symposium, London, J. & A. Churchill Ltd., 1958.
14. THORNER, M. W., ALPERS, B. J. and YASKIN, J. C.: Acute ascending paralysis (Landry's paralysis); clinicopathologic study. *Arch. Neurol. and Psychiat.* 4: 17–42, July 1940.
15. PETERMAN, A. F., DALY, D. D., DION, F. R. and KEITH, H. M.: Infectious neuronitis (Guillain-Barré syndrome) in children. *Neurology* 9: 533–539, Aug. 1959.
16. AUSTIN, J. H.: Recurrent polyneuropathies and their corticosteroid treatment; with 5-year observations of a placebo-controlled case treated with corticotrophin, cortisone and prednisone. *Brain* 81: 157–192, June 1958.
17. BRESSLER, R. and JOHNSON, S. T.: Cushing's syndrome and the Guillain-Barré syndrome. *Ann. Int. Med.* 50: 1298–1303, May 1959.
18. GRANT, H. and LEOPOLD, H. N.: Guillain-Barré syndrome occurring during cortisone therapy. *J.A.M.A.* 155: 252–253, May 15, 1954.

SKIN DEEP?

The skin is of course more than just a covering, to protect the various organs and prevent them from slopping around and looking untidy. It is, amongst other things, a true mirror of the mind, reflecting the emotional battles and frustrations, to which every individual is unavoidably prone.—R. W. B. SCUTT: The Approach of the Naval Medical Officer Toward Patients With Skin Diseases. *Journal of the Royal Naval Medical Service,* Autumn 1959.

The Quality of Military Medical Reports

LIEUTENANT COLONEL PATSY M. FIANDACA, JR., MC, USA

THE ARMY MEDICAL SERVICE annually performs and processes several million medical examinations. Most of these examinations are accomplished at Armed Forces examining stations. The remainder are done in Army hospitals, dispensaries, and other military medical facilities located in the continental United States or overseas.

This office is charged with the responsibility of critically reviewing and processing many of these medical examinations yearly. Final determination of the medical qualifications of applicants for appointment to the Regular Army, the U.S. Military Academy, Army aviation training, marine diving, the Army Nurse Corps, the Army Medical Specialist Corps, and dental and medical intern and residency programs are effected in this office. In addition, the Physical Standards Office reviews medical records and determines medical qualifications of selected applicants for active duty in the Army Reserve, Reserve Officers Training Corps, airborne training, and officers' candidate schools. It also reviews the medical qualifications of applicants for Regular Army promotions, the enlistment and induction of those with prior separation from service by reason of disability, applications of special registrants, and controversial cases of all kinds, as well as many others arising from inquiries and reclamas directed to the President, Selective Service, the Department of the Army, members of Congress, and other Armed Forces and Governmental agencies. This office also reviews and makes appropriate recommendations on retirement and separation cases, cases of members with disqualifying conditions applying for continuance in service, cases of suspended aviators, claims cases, and the like.

In order to permit a full and fair review and evaluation, the medical

---

From Physical Standards Office, Professional Division, Office of the Surgeon General, Department of the Army, Washington, D.C.

records must contain the report of a complete medical examination, accomplished within the scope prescribed in the applicable regulations and recorded on Standard Form 88 (Report of Medical Examination) and Standard Form 89 (Report of Medical History).

Medical officers assigned to the Physical Standards Office are in a position to evaluate critically the quality of examinations attained at various medical installations. Since every personnel action recommended by this office affects the future of the person concerned and the best interests of the Government, the importance of thorough, complete, and properly reported medical records is readily apparent.

The greatest challenge in the area of medical evaluations is the problem of improving the quality of medical examinations and reports submitted for review. There is constant need for continued supervision and guidance at all levels. Surprisingly, 1 out of 4 reports received in this office requires referral to the originating unit for additional essential information. Although it is realized that medical officers in the field do not appreciate having reports returned, it must be recognized that incomplete or inadequate reports make just and final determinations impossible.

For the past 2 years I have participated in an orientation course given to medical examiners newly assigned to Armed Forces examining stations. An extension of the Army Medical Service School Orientation Course for Reserve Officers held at the Army Medical Service School, Brooke Army Medical Center, Fort Sam Houston, Texas, this course is specifically designed to orient Armed Forces examining station medical officers in their assignment and to stress the importance of the quality of medical examinations and reports originating from their examining stations. Since most incoming military personnel are processed through the Armed Forces examining stations situated throughout the United States and its possessions, it is essential that medical examiners be thoroughly indoctrinated in their responsibilities and duties. With these considerations in mind, the orientation course referred to here was established several years ago to elaborate on these responsibilities. Happily, this orientation is beginning to show positive results. Follow-up questionnaires dealing with validity and scope of the course reflect full justification of its establishment and continuance.

It is hoped that other medical examiners will find the dissemination of this information beneficial. It must be stressed again that the report of medical examination is an important document. This is true not only in relation to a man's original entry into the service, but also in connection with all subsequent evaluations of his medical

status, since his medical evaluation may well affect assignment, promotion, separation, and retirement, and in this sense becomes of real monetary interest both to the individual and to the Government.

With the importance of the medical examinations and records established and emphasized, we might cite a few practices that affect the quality of the finished product. We must agree that proper medical examining and reporting is good medical practice. It is obvious that many unnecessary delays and other problems are occasioned by examinations that have not been completed or recorded properly. These situations can be avoided if the following practices, now frequently neglected, are strictly observed:

(1) Check or complete each required item on Standard Form 88 (Report of Medical Examination). An examiner with a comprehensive knowledge of what must be accomplished will adhere to this practice. An annual medical examination, for example, has a scope entirely different from that of a primary flight medical examination. It is the examining officer's responsibility to check the applicable requirements to ascertain that they have been met.

(2) Confirm a diagnosis either by a complete report of consultation or by the performance and recording of appropriate laboratory or roentgenologic data, to include clinical evaluation of the results.

(3) Check for and correct typographic errors on final typed copies.

(4) Elaborate adequately on each item checked positive in the history portion (Standard Form 89) of the examination form. To be sufficient, this elaboration should include the results of indicated examinations and consultations.

(5) Check the number of copies of the examination form to be prepared and forwarded.

(6) Properly identify the examiner signing the report.

(7) Sign the report.

(8) Constantly check the pertinent regulations, including all changes.

The following practices should be discontinued:

(1) Using unauthorized stamps. In general, stamps are objectionable if they fail to provide the opportunity to record *positive* information.

(2) Permitting the use of overprinted forms that show negative results of laboratory findings, roentgenologic reports, or examiner's findings before their actual accomplishment.

(3) Signing blank report forms, assuming that the final typed copies will be completed correctly from the work sheet.

(4) Checking off as accomplished portions of the examination

that in fact were not done, such as temperature, ocular tension, ophthalmologic.

If the following 3 recommendations are observed, most of the unsound practices affecting the preparation of an acceptable medical report will be avoided:

(1) The examiner should have full knowledge and command of the regulations, which provide him with most of the answers. All the pertinent regulations, changes, policy letters, and memoranda should be posted, as these may drastically affect the proper completion of the report. A part of each day should be set aside for reviewing the requirements of these directives, since they relate directly to current military needs.

(2) The examiner should carefully check the final typed copies for content and completeness *before* signing. Blank forms should never be signed.

(3) The medical officer responsible for the final report should give constant and continued supervision to all other phases of the medical examination.

SUMMARY

The significance of thorough medical examinations of military personnel, both for the individual and the U.S. Government, and the subsequent, accurate accounts reflected in the reports of medical histories and medical examinations are explained and discussed. Details regarding specific practices to follow or avoid are included.

UNSOUND THERAPY

Along with our "miracle" drugs, modern medical practice continues to use a large number of useless and possibly even suspect therapies. The initial impetus supplied by poorly authenticated but published claims is not easy to overcome, and unsound therapies continue long as a part of accepted practice, to be dislodged only by something strikingly superior.—WALTER MODELL: The Ethical Obligations to the Nonsubject. (Editorial) *Clinical Pharmacology and Therapeutics*, March-April 1960.

Shipboard Treatment of Venereal Diseases

LIEUTENANT REINHARDT H. BODENBENDER, MC, USNR

VENEREAL DISEASES are not extinct; diagnostic and therapeutic problems still exist. The naval medical officer is confronted aboard ship with a concentrated and unique experience in these diseases and their treatment.

Although hundreds of deployments to the Far East are made each year by home-ported West Coast ships of the Pacific Fleet, a perusal of the literature will fail to guide the medical officer in his treatment of the most common venereal disease, gonorrhea. Numerous treatment schedules have been advocated, but in the main, civilian medical literature de-emphasizes the therapeutic problems, and suggests that penicillin is not only the drug of choice but is moreover infallible. Fiumara and co-workers [1] state: "In Massachusetts we have found that 600,000 units of procaine penicillin G in aqueous suspension in a single dose intramuscularly will give a 95 to 98 per cent cure rate for acute gonorrhea in the male. The 2 to 5 per cent who fail to respond in forty-eight hours to the initial injection are given an additional 600,000 units. There have been no failures with the second injection. When apparent failures were seen, re-exposures were admitted." The sense of security this article engenders is offset by the report of Epstein,[2] who studied 154 cases of acute gonorrhea in American troops in Korea. A 20 percent treatment failure was recorded, and the penicillin treatment failures are explained by the author on the basis of penicillin-resistant strains of *Neisseria gonorrhoeae*.

Interest in the possibility of penicillin-resistant strains of gonococci is also reported from the London Hospital. Employing a single injection of 300,000 units of penicillin, Curtis and Wilkinson [3] found that over 11 percent of 1,116 patients still harbored the gonococcus after treatment. Also, 72 percent of the treatment failures were

From U.S. Naval Hospital, San Diego, Calif. Dr. Bodenbender is now at 2732 7th Street, Moline, Ill.

infected with gonococci resistant to concentrations of penicillin lower than 0.25 units per ml. The authors state that the use of long-acting penicillin such as benzathine penicillin may be a real danger because some patients with gonorrhea may be converted into living test tubes for producing resistant strains of gonococci. It was concluded that following larger doses—600,000 to 1,200,000 units of aqueous procaine penicillin G with or without a booster of crystalline penicillin G—successful therapeutic results in infections with more resistant strains of gonococci could be expected. Also from England, Cradock-Watson and his associates [4] report apparent treatment failures in patients infected with penicillin-resistant strains.

Certainly a quandary is evident: Whereas the conclusions of Fiumara would promote a lethargic and disinterested approach to the treatment of acute gonorrhea, the observations by Epstein and by our English colleagues must stimulate the Navy physician's responsibility to study this venereal disease problem in the Far East. The questions of concern are: (1) Are penicillin-resistant strains of *N. gonorrhoeae* emerging? (2) What role does the "quasi nongonococcal urethritis" play in this over-all problem? (3) What is the drug of choice in the treatment of gonorrhea? (4) How should gonorrhea be treated if initial penicillin therapy does not cure? (5) Is the problem of relapse in reality a problem of reinfection?

MATERIALS AND METHODS

During a recent 5½-month deployment to the Far East, 3 West Coast–based destroyers (DD's), representing 1 destroyer division and including a complement of 722 enlisted men and officers, were utilized as a small isolated study group for the treatment of venereal diseases aboard ship. Each ship's organization provided for 1 experienced hospital corpsman to handle routine sick call. One division medical officer was billeted to these ships and was readily available on the flagship for consultations or emergencies at sea.

Diagnosis. In port all the venereal disease cases were seen by the medical officer after the patient had reported with symptoms to his respective corpsman. While at sea each hospital corpsman was in full command to diagnose all cases; aboard the flagship, however, the medical officer saw each patient and reviewed all smears. Diagnostic facilities aboard a destroyer were very limited: 1 standard microscope, Gram stains, and glass slides comprised the entire armamentarium. Dark field examinations were not done at sea, and cultures were an unheard-of luxury.

The following 85 cases of venereal disease were diagnosed in 83 patients:

Type of venereal disease	*Number of cases*
Gonorrhea	70
Nongonococcic urethritis	7
Chancroid	7
Syphilis	1
Total	85

One sailor contracted both gonorrhea and chancroid, and another was infected with both syphilis and chancroid. These 83 patients, representing 11.5 percent of the entire complement of the division, ranged in age from 17 to 42 years, the greatest number of men being 20 years old. The age distribution was as follows:

Age	*Number of patients*
17	1
18	6
19	10
20	23
21	17
22	8
23	7
24	2
25–42	9
Total	83

The ports of call and the number of patients infected with a venereal disease in each area follow:

Place of contact	*Number of cases*
Okinawa	16
Kaohsiung, Taiwan	10
Hong Kong	18
Sasebo, Japan	20
Yokosuka, Japan	14
Iwakuni, Japan	3
Tokyo, Japan	1
Los Angeles, Calif.	1
Total	83

Treatment. Prior to deployment each hospital corpsman was

instructed in the following treatment regimen for gonorrhea and chancroid:

Treatment of gonorrheal urethritis

I. *Positive diagnosis* (smear):
Ship # 1: 600,000 units of procaine penicillin G every day for 5 days
Ship # 2: 600,000 units of procaine penicillin G every day for 3 days
Ship # 3: 300,000 units of procaine penicillin G every day for 3 days or (alternate cases) 1,500,000 units of procaine penicillin G every day for 3 days.

II. *Penicillin relapse:*
A. If smear mainly gram negative:
1. 600,000 units of procaine penicillin G every day for 5 days; if further relapse:
2. 250 mg of oxytetracycline (Terramycin) hydrochloride by mouth every 6 hours for 5 days; if further relapse:
3. 500 mg of chloramphenicol (Chloromycetin) by mouth every 6 hours for 5 days

B. If smear mainly gram positive:
1. 1.0 gm of sulfisoxazole (Gantrisin) diethanolamine every 4 hours for 5 days

Treatment of chancroid

1.0 gm of Gantrisin or sulfadiazine every 4 hours for 5 days

In addition, all men who acquired a venereal disease were medically restricted to their ships for a minimal period of 30 days and were not allowed ashore until clinically cured and until a blood serologic examination had been performed and reported negative. This prolonged period of medical observation was instituted to allow for adequate follow-up and also to eliminate the factor of reinfection.

RESULTS

Of 68 patients with acute gonorrhea treated initially with penicillin. according to 4 different dosage schedules, 27 were not clinically cured with penicillin alone, resulting in a combined treatment failure or relapse of 39.7 percent (table 1).

It should be noted that even with the highest dosage regimen, i.e., 1,500,000 units of procaine penicillin every day for 3 days, there was still a 14 percent relapse rate; and as the total penicillin dosage decreased, the relapse percentage progressively increased to the point that *all* patients treated with only 900,000 units relapsed.

Typically, penicillin caused the urethral discharge in most patients to disappear, usually after the first dose. However, in 27 patients there was a recurrence of symptoms about 2 weeks after completion of therapy. Since all relapses occurred within the 30-day restriction

Table 1. *Results of initial penicillin therapy in 68 cases of acute gonorrhea on 4 dosage schedules*

Total dose of procaine penicillin G (units)	*No. of cases*	*No. of relapses*	*Relapse rate (%)*
4, 500, 000	14	2	14
3, 000, 000	23	8	35
1, 800, 000	24	10	42
900, 000	7	7	100
Total	68	27	39. 7

period aboard ship, re-exposure was eliminated as a possible cause. All first relapses were treated with oxytetracycline or sulfisoxazole, according to the regimen previously outlined. Of the original penicillin treatment failures, 8 suffered a second relapse. All these patients were eventually cured after treatment with chloramphenicol.

Two cases of acute gonorrhea occurred in patients with past histories of penicillin allergy; one was treated with sulfisoxazole and the other with oxytetracycline. Both responded without relapse.

All patients with chancroid treated with sulfisoxazole or sulfadiazine responded to treatment.

The 7 patients with the diagnosis of nongonococcic urethritis reported to sick bay with a purulent urethral discharge 3 to 6 days after sexual exposure. Diagnosis was determined on the basis of at least 2 gram-stained urethral smears showing both gram-positive and gram-negative organisms but without demonstrable gonococci. One of these patients was treated with sulfisoxazole and the other with 600,000 units of procaine penicillin every day for 5 days. No relapses were noted in this small group.

CASE REPORTS

The following case is an excellent example of some diagnostic, therapeutic, and follow-up problems facing Navy medical officers at sea.

CASE 1. A 22-year-old seaman apprentice was first seen at sick call aboard ship on 27 April 1959, with penile lesions resembling chancroid. At that time the ship was at sea on local operations. Because of limited laboratory facilities aboard ship, diagnosis and treatment were withheld, and only hygienic measures were instituted pending the ship's return to port in 2 days. On the first day in port the patient went AWOL before any laboratory work could be done. When he returned to the ship 3 weeks later, the lesions had cleared. He gave the his-

tory that he had received treatment in the form of "shots" from a civilian physician but had not been told the exact diagnosis.

He again reported to sick bay on 16 June 1959, while the ship was on the high seas deployed for the Far East, with the complaint of a rash on the palms of both hands and soles. The dermatitis consisted of circumscribed, nonpruritic, papulosquamous lesions suggestive of secondary syphilis. Since the ship was again at sea, laboratory confirmation could not be obtained. On arrival at Guam 4 days later a serologic test was negative.

On 8 July 1959, while the ship was in Buckner Bay, Okinawa, the patient again reported to sick bay, this time with a recurrence of the original penile lesions. Now a dark field examination, smear, and serology were done at the U.S. Army Hospital. The dark field examination was reported as negative, but the smear was diagnostic of chancroid with secondary staphylococcic infection. The patient was treated with chloramphenicol and sulfisoxazole for 1 week. Blood was drawn for serologic examination, but the report, which was positive, did not reach the ship until its arrival at Sasebo, Japan, 1 month later. The patient was immediately transferred to the station hospital in Sasebo with the diagnosis of latent syphilis, seropositive only. At this time the penile lesions had again cleared, and the physical and neurologic examinations were within normal limits. A serologic test on the spinal fluid was negative. Gold curves were not reported. Treatment consisted of 2,400,000 units of benzathine penicillin G (Bicillin). The patient returned to the ship 10 days later and completed the rest of the cruise without further complaints.

According to this man's official Navy medical record his diagnoses are definite: chancroid of the penis, and latent early syphilis, seropositive only. Some medical doubt, however, may be raised concerning the diagnostic validity of secondary syphilis in the light of the first negative serologic test.

Incubation periods for acute gonorrhea were normally found to be between 3 and 6 days. The next case is of interest because the patient had an unusually long incubation period.

CASE 2. A 17-year-old seaman apprentice reported to sick bay with a purulent urethral discharge 20 days after admitted sexual exposure in Yokosuka, Japan. The prolonged incubation period was doubted until it was learned that the patient had received 5 injections of 600,000 units of procaine penicillin G for acute tonsillitis just before he flew from the States to join the ship in Japan.

The suppression of symptoms by previous pencillin therapy and the axiomatic importance of a careful medical history are again emphasized.

DISCUSSION

Harrison [5] states that a large number of strains of gonococci have become resistant to sulfonamides but that "only rarely have gonococci been reported resistant to penicillin. The gonococcus is *exceedingly susceptible* to this antibiotic, which at present is the drug of choice." Two injections of 300,000 units of procaine penicillin are advocated.

It becomes evident from the recent literature, however, that our treatment of acute gonorrhea is far removed from this optimistic textbook picture. Penicillin treatment failures of 11 percent,[3] 20 percent,[2] and—in this shipboard study—39.7 percent are certainly cause for alarm, concern, and speculation.

Two possible explanations for this disparity can be tendered at this time: one is that certain strains of the gonococcus are definitely becoming resistant to penicillin, and the other is that this whole problem is not simply that of treating a single infective organism. The diagnosis of nongonococcic urethritis is indeed nebulous—based technically on a negative observation and a characteristically prolonged incubation period, which according to Graham [6] is rarely shorter than 14 days. The 7 cases thus classified in this study were probably in reality gonorrheal, since the incubation periods were between 3 and 6 days. Because of shipboard technics, however, with most of the microscopic work performed on the high seas and the observer hampered many times by 20- to 40-degree rolls and continuous pitching of the ship, positive identification of the gonococcus could not be made. The successful pencillin treatment of these patients also raises further doubt of the original diagnosis, since penicillin is considered [5,6] of no value in the treatment of nongonococcic urethritis. It may be speculated that most of the cases included in this report were caused by mixed urethral organisms; and that the penicillin-sensitive bacteria were initially eradicated, leaving the nonsensitive or penicillin-resistant ones to multiply and become the eventual cause of the treatment failure or relapse.

At this time penicillin is still the drug of choice for the initial treatment of acute gonorrhea. The dosage schedule seems to be the most important factor, however, as evidenced by the present study, in which the percentages of relapse varied inversely with the total dosage of penicillin given. It appears imperative that immediate high blood levels of penicillin be attained during this initial treatment of acute gonorrhea. I advocate a schedule of 1.5 million units of aqueous procaine penicillin G intramuscularly every day for at least 5 days. If a relapse occurs, oral administration of a broad-spectrum antibiotic such as oxytetracycline should be instituted, with chloramphenicol held in reserve.

The role of reinfection was eliminated from this study because of the extended and closely controlled treatment and observation period of 30 days aboard ship. I highly recommend this practice to all medical officers afloat; the shipboard treatment of venereal disease is becoming complex enough without adding another variable that might further delay a cure.

562174 O—60- —6

SUMMARY

Shipboard medicine in the Navy still has a fertile and challenging field in the epidemiology and treatment of venereal diseases. During a recent 5½-month Far East cruise aboard 3 naval destroyers, 85 cases of acute venereal disease were diagnosed and treated. In 68 cases of acute gonorrhea treated initially with penicillin, employing 4 dosage schedules, a total treatment failure of 39.7 percent was noted. The percentage of relapse varied inversely with the total dose of penicillin given. The roles of nongonococcic urethritis and the penicillin-resistant gonococcus are discussed. Penicillin is still the drug of choice in the treatment of acute gonorrheal urethritis, but the author advocates very high doses of aqueous procaine penicillin G.

ACKNOWLEDGMENT: For their competent efforts under duress of the high seas, the author is indebted to the following hospital corpsmen: L. B. Clark, HMC; R. Tomlin, HMC; H. B. Elder, HM1; and J. Zinich, HM1.

REFERENCES

1. Fiumara, N. J., Appel, B., Hill, W. and Mescon, H.: Venereal diseases today. *New England J. Med.* 260: 863–868, April 23, 1959; 917–924, April 30, 1959.
2. Epstein, E.: Failure of penicillin in treatment of acute gonorrhea in American troops in Korea. *J.A.M.A.* 169: 1055–1059, March 7, 1959.
3. Curtis, F. R. and Wilkinson, A. E.: Comparison of in vitro sensitivity of gonococci to penicillin with results of treatment. *Brit. J. Ven. Dis.* 34: 70–82, June 1958.
4. Cradock-Watson, J. E., Shooter, R. A. and Nicol, C. S.: Sensitivity of strains of gonococci to penicillin, sulphathiazole, and streptomycin. *Brit. M.J.* 1: 1091–1092, May 10, 1958.
5. Harrison, T. R. and others (editors): *Principles of Internal Medicine*, ed. 3, Blakiston Co., New York, N.Y., 1958 p. 874.
6. Graham, R. S.: Nongonococcal urethritis, Enclosure 1, BUMEDINST 6222.1, July 29, 1952. (From the Preventive Medicine Division of the Bureau of Medicine and Surgery, Navy Department, Washington, D.C.)

THE WORD IS THE THOUGHT

There is no excuse for bad writing, which is generally a symptom of poor thinking.—George Sarton: Notes on the Reviewing of Learned Books. *Science*, April 22, 1960.

Osteochondrosis of the Tarsal Scaphoid (Köhler's Disease)

LIEUTENANT COLONEL STROTHER B. MARSHALL, USAF, MC

THE CLINICAL PICTURE of Köhler's disease of the tarsal scaphoid rapidly became recognized as a distinct entity, self limited and without sequelae, after Köhler in 1908 described 3 cases of "a common, apparently previously unknown disease of certain bones in children."[1] In all 3 cases the tarsal navicular was involved in a spontaneous degenerative process, well demonstrated roentgenologically. One patient exhibited the additional phenomenon of osteochondritis of the patella. By 1924 Kidner and Muro[2] were able to collect 154 cases. Further reports in the English language followed: in 1927 by Speed;[3] in 1928 by Ely;[4] and in 1937 by Karp,[5] who gave an excellent review of 45 cases over a 10-year period at the Boston Children's Hospital. The 1958 study of Waugh[6] from Nottingham, England, represents the most recent review and the first comprehensive attempt to investigate the etiology of this disease.

Although not atypical from the standpoint of the larger series of Karp and Waugh, the following cases are reported to illustrate the striking clinical pictures the disease may present and the difficulty in diagnosis occasionally brought about by the lack of relationship between clinical and roentgenographic findings.

CASE REPORTS

CASE 1. A 3-year-old boy was admitted to this hospital 25 January 1959 because of pain and swelling of the left foot of 2 days' duration. The child had developed chickenpox 6 days before admission and had been treated with aspirin because of persistent low-grade fever. During the 48 hours preceding admission, swelling, erythema, and tenderness had developed rapidly over the medial aspect of the left foot and ankle. The child refused to bear weight. There was no history of

From 2500th USAF Hospital, Mitchel Air Force Base, N.Y. Dr. Marshall is now at 137 Broad Street, Claremont, N.H.

trauma. He had previously been in excellent health and his system review was negative.

Physical examination on admission revealed a fretful child with temperature of 100°F and pulse 100. The skin was covered with the classic cutaneous lesions of chickenpox. The remainder of the examination was not remarkable except for the swelling, erythema, and tenderness over the medial aspect of the left foot and ankle. Complete blood count and urinalysis were within normal limits. The corrected sedimentation rate was 24 mm/hr. Throat culture demonstrated normal flora, and the chest roentgenogram was not remarkable. Roentgenograms of the ankles and feet (fig. 1) showed the left scaphoid somewhat smaller than the right, but of normal contour and density. The child responded to treatment with bed rest and hot packs to the left ankle, with rapid subsidence of the swelling. He was discharged after 4 days without a definite diagnosis.

Figure 1 (case 1). Initial roentgenograms of feet. Involved left scaphoid is smaller than right, but of normal contour and density.

At home, as long as he remained at rest, he continued to be relatively asymptomatic. However, intermittent swelling and low-grade fever recurred. He was placed in a walking cast 3 April 1959 because of recurrence of swelling and pain. Examination of the foot at this time revealed no erythema or heat, but a firm, rubbery mass over the medial dorsal aspect of the left foot, well defined proximally but fading into the soft tissues distally. Roentgenograms at this time showed little change in the appearance of the left scaphoid, which remained smaller than

Figure 2 (case 1). Photomicrograph of biopsy specimen. Profuse infiltration of plasma cells and lymphocytes is noted, particularly in perivascular spaces.

the right and perhaps slightly more dense, but with no evidence of fragmentation or irregularity.

Because of the questionable nature of the mass, biopsy of the soft tissue tumor was performed 21 April 1959. The tumor mass lay just below the subcutaneous tissue and had a granulomatous appearance, with rather clearly defined margins. It was seen to involve all major structures in the area and to extend to the tarsal articular surfaces. After a generous biopsy had been taken, the wound was closed and a cast applied. One week after sutures were removed, this was changed to a walking cast, which the child wore for 3 weeks. He has subsequently been totally asymptomatic. Roentgenograms 11 months after the onset of symptoms showed distortion of the scaphoid, with flattening and fragmentation, in spite of absolute lack of symptoms for the previous 6 months.

The biopsy specimen (fig. 2) was rather remarkable. Actively proliferating fibrous connective tissue was noted, with edema and a profuse infiltration of plasma cells and lymphocytes, tending to lie in perivascular channels.

CASE 2. A 25-month-old boy was first seen in the surgery clinic of this hospital on 19 October 1959. For the previous 3 weeks the child had been limping and exhibited spontaneous swelling in the region of the left scaphoid. The amount of swelling had fluctuated during the day, being more marked with activity. There was no history of trauma or recent febrile illness. On physical examination (fig. 3) marked swelling, tenderness, and erythema were noted over the left scaphoid.

Roentgenograms revealed typical changes of Köhler's disease of the left scaphoid, with increase in density, irregularity, and flattening (fig. 4). A walking cast was applied and maintained for 5 weeks. Reexamination at that time showed very slight pinpoint tenderness remaining over the scaphoid, with no swelling. Two weeks later the child was totally asymptomatic.

DISCUSSION

Köhler's disease of the tarsal scaphoid affects children within the first decade, the average age of onset being approximately 4½ years. Boys are affected more commonly than girls (4 to 1, Waugh,[6] 6.5 to 1, Karp[5]) and are more likely to be somewhat older when symptoms first appear. Bilaterality is unusual, being reported in most series as occurring in less than 10 percent of cases. A history of preceding trauma is usually vague. The onset of the disease is spontaneous, typically a lameness in one foot, accompanied by pain and the complaint that the shoe hurts. Pain, sharply localized over the scaphoid, disappears initially with rest, but recurs with activity. Swelling, tenderness, heat, and redness in varying degrees follow in most cases. There is usually an intermittent fever. As demonstrated by the first case, the inflammatory response accompanying the onset of this disease can be quite striking. Acute osteomyelitis, septic arthritis, and tu-

Figure 3 (case 2). Appearance of left foot when first seen, with marked swelling and tenderness over scaphoid.

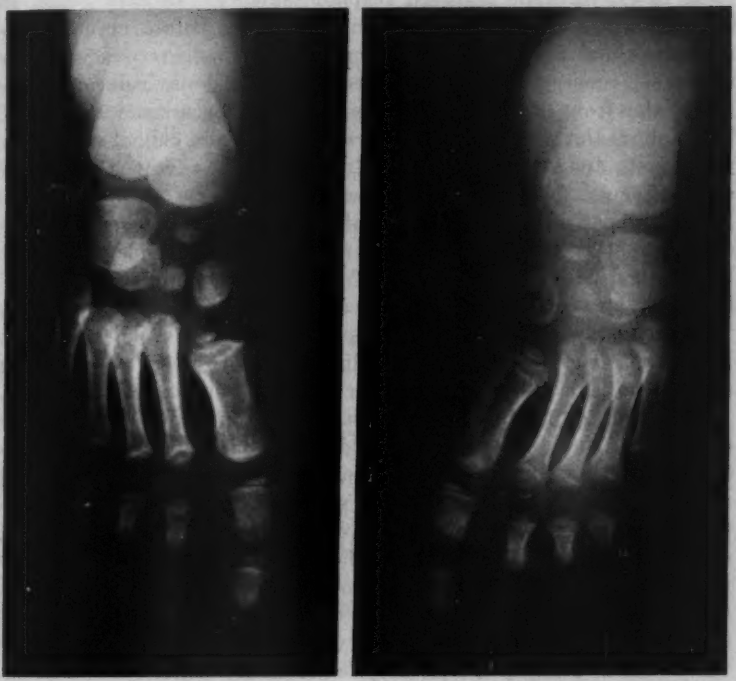


Figure 4 (case 2). Initial roentgenograms. Left navicular is somewhat smaller than right and somewhat mottled and irregular in density.

berculosis present differential possibilities. With rest, all clinical signs and symptoms subside in a matter of a few weeks. Recurrence or sequelae have not been reported.

Roentgenographic findings, when typical, confirm the diagnosis. The usual picture, present from the onset of symptoms, as seen in case 2, is of a flattened navicular, with patchy areas of increased density and loss of trabecular pattern; the osseous nucleus appears compressed. The less common, second type of initial roentgenographic picture is more confusing, as in case 1. Although remaining smaller than the navicular of the normal foot, the ossified portion of the navicular retains its shape and gradually increases in density. In case 1, definite roentgenographic changes did not occur for several months, by which time the child had clinically fully recovered. Earlier changes than actual fragmentation should be sought. Difference in size

between the normal and abnormal bones was an early finding in both these cases, with the involved scaphoid smaller. In case 1 loss of homogeneity and increase in density followed, before actual fragmentation and absorption. Although symptomatic recovery occurs in weeks, roentgenographic regeneration of the navicular in both types takes from 1 to 5 years, with an average of 2 years and 9 months.[5] Throughout this period the space between talus and cuboid retains its usual span, and indeed, in the final outcome, the involved navicular is indistinguishable from its normal counterpart.

In their pathologic descriptions of the scaphoid bone removed for one or another reason during the acute phase of Köhler's disease, Lecène and Mouchet [7] and Speed [3] concur that the process is one of central avascular necrosis. The central portion of the bone is soft, "like cream cheese," [3] and microscopically avascular necrosis without inflammation is the consistent finding. The gross size of the bone remains normal by virtue of its outer coat of normal cellular cartilage.

The pattern of this disease, with its spontaneous onset, acute course, and full recovery, early led to its inclusion with Osgood-Schlatter disease, Legg-Calvé-Perthes' disease, Sever's apophysitis of the os calcis, Köhler's and Freiberg's epiphysitis of the second metatarsal head, Scheuermann's epiphysitis of the vertebral epiphysis, and many others in the broad classification that Harbin and Zollinger termed "osteochondritis of the growth centers." [8] These authors assumed a common etiology for all these syndromes, making a division only into primary and secondary types, depending upon whether the involved epiphysis is a primary or secondary center of ossification. Köhler's disease of the scaphoid would thus be thought of as a primary osteochondritis, along with the rare disease in the patella, described by Köhler,[1] and the even rarer osteochondritis of the vertebral body described by Calvé in 1925.[9]

The first attempt at understanding the mechanism for the central avascular necrosis in Köhler's disease was made by Karp,[5] who followed serial roentgenograms of normal feet in girls and boys from 6 months to 4 years of age. A similar study was later made by Waugh.[6] Both authors concluded that the average age of ossification of the scaphoid in girls is between 18 and 24 months, and for boys, between 30 and 36 months. Abnormalities of ossification are common, consisting of minor irregularities in size and shape with, at times, gross changes apparently indistinguishable from those seen in Köhler's disease. The abnormalities are more common in boys and are more frequent in naviculars that ossify later than usual. Both authors noted that clinical Köhler's disease appears only after ossification has begun.

To date, Waugh [6] has been the only investigator to study the vascular development of the normal scaphoid. By injection technics he was able to demonstrate that the scaphoid has a profuse perichondral vascular network on the nonarticular surfaces. Normally, 5 or 6 arteries from this plexus penetrate into the central ossification center, but occasionally a single dorsal or plantar artery may supply the whole nucleus. This rich perichondral vascularity apparently retains the integrity of the cartilage in Köhler's disease at a time when, for some yet unknown reason, the delicate penetrating vessels become inadequate to supply the nutritional needs of the ossification center.

Two questions thus remain unanswered. What is the primary factor in this loss of vascularity? What is the reason for the inflammation? Both phenomena are common to all the "osteochondroses," and their mechanisms remain speculative.

SUMMARY

Two cases of Köhler's disease of the tarsal scaphoid are presented. In one case, persistent localized swelling and confusing roentgenographic findings led to biopsy of the soft tissue mass. The literature concerning this disease is reviewed in an attempt to define the known and unknown aspects of its etiology.

REFERENCES

1. Köhler, A.: Über eine häufige, bisher anscheinend unbekannte Erkrankung einzelner kindlicher Knocken. *Münschen. med. Wchnschr.* 55: 1923–1925, Sept. 15, 1908.
2. Kidner, F. C. and Muro, F.: Köhler's disease of tarsal scaphoid or os naviculare pedis retardatum. *J.A.M.A.* 83: 1650–1654, Nov. 22, 1924.
3. Speed, K.: Köhler's disease of tarsal scaphoid bone. *Tr. Am. Surg. Assoc.* 45: 179–189, 1927.
4. Ely, L. W.: Köhler's disease. *Arch. Surg.* 16: 560–568, Feb. 1928.
5. Karp, M. G.: Köhler's disease of tarsal scaphoid; end-result study. *J. Bone & Joint Surg.* 19: 84–96, Jan. 1937.
6. Waugh, W.: Ossification and vascularization of tarsal navicular and their relation to Köhler's disease. *J. Bone & Joint Surg.* 40B: 765–777, Nov. 1958.
7. Lecène, P. and Mouchet, A.: La scaphoïdite tarsienne (anatomie pathologique et pathogénie). *Revue D'Orthopédie* 11 (series 3): 105–112, March 1924.
8. Harbin, M. and Zollinger, R.: Osteochondritis of growth centers. *Surg. Gynec. & Obst.* 51: 145–161, Aug. 1930.
9. Calvé, J.: Localized affection of spine suggesting osteochondritis of vertebral body, with clinical aspect of Pott's disease. *J. Bone & Joint Surg.* 7: 41–46, Jan. 1925.

Blood Bank Accreditation

An Aid to the Air Force Blood Program

FIRST LIEUTENANT JOHN D. VOORHEES, USAF, MSC

FOR BOTH PROFESSIONAL AND LOGISTIC REASONS, the need for accreditation of the blood bank at this Air Force base has been apparent for some time. In the Tampa area, as is true in many localities, blood-banking services are not performed by the American National Red Cross, but by a community blood bank, operating independently—yet within the sphere—of a state organization. Among member banks, all of which maintain identical standards, blood may be transferred freely as required. A bank not a member of the group, however, may only *withdraw* blood from the association. This must then be repaid, either on a cash basis or by providing a suitable donor.

Since its opening in 1947, the MacDill blood bank has drawn and processed its own blood. With such a large potential source of donors, it would seem that the supply would far exceed the demand. We have found, however, that this is not always the case. Frequently, the time expended in obtaining donors for a particular patient is not justified. In addition, a number of the local municipal banks pay their donors. This is indeed powerful competition in the Air Force community. Thus, as the demand for blood at this base remained fairly constant, the supply fluctuated, seemingly at the most inconvenient times. For these reasons, we felt accreditation and membership in the Florida state association would obviate some of the problems, since we would not be left totally dependent on our own resources.

Today, in most areas, there are only 2 organizations for accreditation of the blood bank: a national organization, the American Association of Blood Banks; and a State organization—the Florida Association of Blood Banks.

From U.S. Air Force Hospital, MacDill Air Force Base, Fla. Presented 15 February 1960 at the USAF Medical Laboratory Symposium, Andrews Air Force Base, Washington, D.C.

SPECIFICATIONS FOR ACCREDITATION

Before accreditation, a bank requesting membership in either organization is subject to a very thorough and stringent inspection. The standards to be met during this inspection, either by the state or national organization, are contained in a publication of the Joint Blood Council, Inc., and the American Association of Blood Banks, entitled "Standards for a Blood Transfusion Service." [1] The American Association of Blood Banks is interested in all phases of blood banking, whereas the primary concern of the state association is in drawing and storage procedures. It is well to emphasize that these standards do not in any way conflict with those of the medical services of the Armed Forces. Upon examination, the standards are found to be basic and universal, establishing practices that should be used in any good blood bank. The only differences we have found have been administrative in nature. These can easily be resolved to the satisfaction of both parties. To a great extent, the standards are a condensation of the American Association's manual on blood bank technic,[2] which should be present in, and used by, any blood bank.

The inspection, conducted by a person or persons designated by the state association, covers all phases of blood banking. It is both oral and practical in nature and is of several hours' duration. The inspectors interview not only the supervisors, but also the personnel who perform the routine work, in order to obtain as true a perspective of the blood bank operation as possible. Following the inspection, the bank director is notified whether the bank is to be associated with the group for a 1-year period. He is also informed of any recommendations of the state association. At this point it is well to note that the state association only *recommends* changes; however, noncompliance can result in reinspection or suspension from membership.

ADVANTAGES OF BLOOD BANK MEMBERSHIP

The advantages of membership have been many and have done much to alleviate some of our earlier problems. We can now exchange blood through the state clearing house on a one-for-one basis. We do not maintain stocks of packed cells, frozen plasma, or rare blood group combinations. Such stocks can be obtained from the municipal blood bank and the necessary credits transferred to cover such transactions. An excess of particular types or groups of bloods can be put into circulation, allowing us to maintain adequate stocks without danger of their expiration. We do not prepare plasma, as this formerly resulted in a substantial loss of expired blood. Currently our outdated

blood, which is less than 25 days old, is processed by the municipal bank and our account is credited.

In 1959, a faulty thermostat resulted in the freezing of all blood in the MacDill blood bank. This was discovered early in the morning; by 0900 our bank had been restocked from other member banks and the "business as usual" sign was up on the door. Last year a hospital in North Africa requested a unit of plasma from us for a hemophiliac. This was provided by a member bank in Miami and was en route, in a matter of 2 hours, to the patient.

The mutual aid plan, however, is not a cure-all for the blood bank. Although all member banks must stand ready to aid one another, excessive demands cannot be made or honored. Help is given insofar as is possible, but the individual bank cannot afford to deplete its own stocks to a dangerous level. Regardless of the size of the donor file, difficulty will be encountered at various times in obtaining particular types of blood. Although the member bank must function as an independent unit, aid can be received from other members, but not to the extent of excessive inventories.

An excellent feature of the association lies in the reference and consultation services that it offers. At present there are many reference laboratories whose names are familiar to everyone in blood banking that perform services either gratis or for a fee. The American Association of Blood Banks maintains a referral laboratory at minimum cost. In addition, the Association and many of the large municipal banks maintain central files of donors of rare blood groups and blood group combinations. Member banks are encouraged to correspond with the central office, which acts as a clearing house, forwarding correspondence to the member most likely to be of assistance to the inquirer.

The accredited blood bank can make substantial progress in the promotion of good community relations and the fostering of good will for the Air Force. Although the accredited Air Force blood bank must, by regulation and nature, remain an independent agent, in numerous instances it can obtain valuable assistance from other local banks.

It has been my feeling for a number of years that the services offered by the Air Force blood bank or laboratory must be equal, or superior, to those provided by its civilian counterpart. A system of inspection assists in providing the best possible service and points the way toward the ultimate goal of excellence. I do not wish to imply that supervision or inspection is any guarantee of quality, which is dependent upon the ability of the individual technician. A bank cannot

function properly *only* on inspection day and expect to provide superior blood banking service. Strict and continuing adherence to the standards required for accreditation will greatly assist the blood bank in its pursuit of excellence.

SUMMARY

The specifications for and the advantages of blood bank accreditation by a State organization are outlined. Standards of membership in such an association are basic and universal, and differ from those of the medical services of the Air Force only in administrative details. The advantages are numerous: Stocks of packed cells, frozen plasma, and rare blood groups need not be maintained, losses from outdated blood are minimized, reference and consultation services are available. The importance of a system of inspection and of strict adherence to the standards required for accreditation are emphasized.

REFERENCES

1. Standards for a Blood Transfusion Service. Prepared jointly by the Scientific Committee of the Joint Blood Council, Inc., and Standards Committee of the American Association of Blood Banks. American Association of Blood Banks, Chicago, Ill., 1958.
2. American Association of Blood Banks. *Technical Methods and Procedures*, rev. ed. Burgess Publishing Co., Minneapolis, Minn., 1956.

OVERSPECIALIZATION

Despite the obvious need for a greater supply of family physicians, and despite the just as obviously expressed desire of the American people for an increase in the supply of family physicians who will assume this total continuing responsibility for the health of the individual and his family, there is incontrovertible evidence to prove that our present system of medical education and our present system of hospital organization are contributing to the demise of the general practice rather than to its survival.—W. B. Hildebrand and John S. De Tar: The Relationship Between the General Practitioner and the Specialist. *Minnesota Medicine*, November 1959.

Studies in Human Isolation I. Perceptual Findings

SANFORD J. FREEDMAN, PH.D.
MILTON GREENBLATT, M.D.

SINCE THE PIONEERING WORK of Hebb and his students at McGill University [1–4] on the sensory and social isolation of human beings, a number of studies have been reported under the rubric "sensory deprivation." The numerous variables involved and the marked differences in experimental procedures make it extremely difficult to compare these studies or even to be sure that all of the experimenters were concerned with the same phenomena. Most of the reports in the literature, however, can be assigned to one or the other of 2 rather discrete attempts: (1) to reduce the absolute level of sensory input to a minimum, which we shall call "deprivation";[5,6] and (2) to eliminate temporal and spatial variation from the sensory input,[4,7] which we shall call "nonpatterning." The experiments have usually involved restriction or occlusion of visual, auditory, and kinesthetic inputs. In addition, a significant aspect of both kinds of situations as described in the literature is "social isolation," although the extent of isolation varies.

The most striking finding in these experiments is that radical changes occur under what appear to be relatively innocuous conditions. Some of the published reports concentrate upon perceptual aberrations; others restrict themselves, more or less, to changes in ego functioning: namely, depersonalization, hallucinations, delusions, or changes in the body image.

The original studies in this area [1] were done at McGill University between 1951 and 1954.

From the Department of Psychiatry, Harvard Medical School, and Massachusetts Mental Health Center, Boston, Mass. This report is a revised and expanded version of WADC Technical Report 59–266 prepared under U.S. Air Force Contract AF 33(616)–5663 and reprinted with permission of the Aerospace Medical Laboratory, Wright-Patterson Air Force Base, Ohio.

"Twenty-two male college students were paid to lie on a comfortable bed in a lighted cubicle 24 hours a day with time out for eating and going to the toilet. During the whole experimental period they wore translucent goggles which transmitted diffuse light but prevented pattern vision. Except when eating or at the toilet, the subject wore gloves and cardboard cuffs, the latter extending from below the elbow to beyond the fingertips. These permitted free joint movement but limited tactual perception. Communication between subject and experimenters was provided by a small speaker system, and was kept to a minimum. Auditory stimulation was limited by the partially soundproof cubicle and by a U-shaped foam-rubber pillow in which the subject kept his head while in the cubicle. Moreover, the continuous hum provided by fans, air-conditioner and the amplifier leading to earphones in the pillow produced fairly efficient masking noise."

The subjects—who remained in the cubicle for only 2 or 3 days—reported visual "hallucinations" that were frequently repetitive and strikingly vivid. There were, in addition, reports of depersonalization and changes in the body image. Intelligence test performance was impaired during and immediately following perceptual isolation.[2] Next, 3 of the experimenters went into the cubicle for 6 days. They reported [4] the following monocular and binocular effects:

"(1) there was fluctuation, drifting and swirling of objects and surfaces in the visual field; (2) the position of objects appeared to change with head or eye movements; (3) shapes, lines, and edges appeared distorted; (4) after-images were accentuated; (5) colours seemed very bright and saturated, and there seemed to be an exaggeration of contrast phenomena."

It was concluded that "normal visual function is dependent upon an optimum range of patterned visual stimulation."[3]

Using similar but somewhat less stringent conditions with severe psychoneurotic patients, Azima and associates [8–10] described a wealth of hallucinations, feelings of depersonalization, and changes in the body image. They did not discuss perceptual changes. Two of their subjects, obsessive-compulsives, became acutely psychotic, requiring electroshock.

Goldberger and Holt [7, 11] used a similar situation with college students for an 8-hour period. More than half of their 14 subjects reported visual images that "were unusual in their sudden spontaneous appearance, their vividness and, in some instances, their 'meaningless' content." The principal interest of these experimenters was to use the situation to encourage primary process thinking.

Lilly [5] addressed himself to the problem, "Is the healthy ego independent of reality or dependent on some fashion, in some degree, on exchanges with the surroundings to maintain its structure?" He attempted to reduce the absolute intensity of all physical stimuli in the following manner:

"The subject is suspended with the body and all but the top of the head immersed in a tank containing slowly flowing water at 34.5° C., wears a blacked-out mask (enclosing the whole head) for breathing, and wears nothing else. The water temperature is such that the subject feels neither hot nor cold. The experience is such that one tactually feels the supports and the mask, but not much else; a large fraction of the usual pressures on the body caused by gravity are lacking. The sound level is low; one hears only one's own breathing and some faint water sounds from the piping. . . . After the initial training period, no observer is present. Immediately after exposure, the subject writes personal notes on his experience."

The experience is described as enjoyable and producing "hallucinations" within a few hours.

Vernon and co-workers [6,12,13] have kept subjects in a soundproof, blacked-out room for as long as 72 hours; these subjects, however, were free to move about in the room. Impairment of motor coordination and changes in galvanic skin resistance, but no significant perceptual changes or hallucinations are reported.

Ruff and Levy [14,15] have also isolated Air Force pilots and some nonflying personnel in a dark, soundproof chamber for as long as 7 days. Subjects were free to move around, fed themselves, and attended to their own toilet, although instructions included a request to restrict the amount of activity. The situation was often found to be stressful and the authors [14] conclude that "meaningful structuring of experience is necessary for adaptation to drastic alterations in environment." Neither hallucinations nor perceptual distortions were described.

Cohen and co-workers [16] used a small acoustic chamber. The subject was asked "not to move, speak, or make noises. No mention was made when he would be released." Hallucinatory-like activity and sometimes severe anxiety were reported within a few hours.

The principal difference between this study and the 2 preceding ones is in the amount of motility allowed the subjects; this difference may be crucial as far as the production or nonproduction of hallucinatory-like experiences is concerned. It is worth noting that Goldberger and Holt's subjects,[7] who also hallucinated easily, were instructed to "try not to move any part of your body unless you find it absolutely necessary."

Finally, one study, different from all the others because of the severe physical restraint imposed, is reported by Solomon and his associates.[17,18] Locked into a tank-type respirator for as long as 30 hours, subjects reported pseudosomatic delusions, illusions, and "hallucinations"; no perceptual changes were described.

It is difficult to make comparisons among these various studies, because of differences in procedure, technics, subjects, and theoretic orientation. We do not know, for example, whether perceptual dis-

tortions would have been found in subjects who were not tested. Furthermore, all the studies were exploratory in nature and sometimes not very rigorously carried out. Nowhere has there been a systematic attempt to manipulate variables to determine what aspects of the "sensory deprivation" situation are crucial to the production of observed effects. As Goldberger and Holt [7] emphasize, "The general effects we observed are the result not solely of perceptual isolation, deprivation or lack of variation, but of the *total* experimental situation."

AIMS OF THIS RESEARCH

Of the many effects reported, this study will deal primarily with 2 types: (a) perceptual distortions (part I) and (b) "hallucinations" (part II). It would be interesting to know whether the production of these 2 kinds of effects is related, i.e., do they necessarily or usually occur together, as would seem to be suggested by the reports of Heron and Bexton? [1,4] In addition, one might want to know whether any of the obvious differences in experimental procedure were related to the production of these effects.

Table 1 summarizes reports of "hallucinations" by 6 groups of experimenters according to conditions of motility and vision. A perusal of this table suggests that "hallucination" production may be related to (a) restricted motility, (b) a homogeneous, diffuse visual field, or (c) both. The data give no clear answer, but both restricted motility and type of visual field seem to be crucial variables. One would want to find out, then, what would result if the same experimental situation were replicated with variations in these parameters.

The present research was an attempt to answer specifically these 2 questions: (1) What is the relationship between perceptual distor-

Table 1. ***Reports of hallucinations under varying conditions of motility and vision (a)***

Investigators	*Motility*	*Visual field*	*Hallucinations*
Wexler et al.[18]	Restricted	Montonous, dim light	Yes
Heron et al.[4]	Restricted	Homogeneous, diffuse	Yes
Goldberger and Holt [7]	Restricted	Homogeneous, diffuse	Yes
Cohen et al.[16]	Restricted	Blackout	Yes
Vernon et al.[13]	Free	Blackout	i. None ii. Minimal
Ruff and Levy [14]	Free	Blackout	Minimal

562174 O—60——7

tions and "hallucinations" (and other cognitive effects) in a sensory deprivation experiment? (2) What is the result (in terms of these 2 kinds of effects) of varying the nature of the visual input?

Thus, this research sought to describe and to measure perceptual and cognitive distortions and disorientations induced by (a) nonpatterned visual and auditory input combined with social isolation, (b) visual deprivation (blackout) combined with auditory nonpatterning and social isolation, and (c) social isolation alone.

METHOD AND PROCEDURE

Subjects

Subjects in the main experimental groups were paid, volunteer college students recruited through the student employment office and screened to eliminate those who seemed particularly "unstable." Only 1 subject was discarded on this basis. Six others, however, were eliminated in advance from the main experimental groups because of personality deviations; they were studied separately in an effort to obtain data on the relationship of personality to sensory deprivation. Screening was based on psychiatric interviews and autobiographic information.

In order to limit the number of subject variables, further restrictions were imposed as far as practical: For the most part, subjects were all undergraduates at the same university, personally unknown to the experimenters, not majoring in psychology, and in the upper third of their classes scholastically. Several prospective subjects were discarded because of "professional" participation in a number of psychologic experiments or in similar experiments. In spite of a few exceptions to these rules, the resulting main experimental groups were fairly homogeneous. There were 27 male and 3 female subjects in the main experiment, with an age range of 17 to 28 years and a mean age of 20.8 years.

Four of these subjects were run in both of the 2 experimental conditions to obtain comparative data on "deprivation" and "nonpatterning."

Situation—Main Experimental Groups

The 30 subjects were divided into the following groups:

1. *The "nonpatterned" or diffuse light group* (10 subjects) received psychiatric interviews and psychologic tests before and after an 8-hour experimental session. Galvanic skin resistance (GSR) and electrocardiogram were recorded intermittently, and regular behavioral ob-

servations were made. Before the first interview, subjects had received a form briefly describing the conditions of the experiment. At the beginning of the experimental session they were instructed to report thoughts, feelings, sensations, dreams, images, and other phenomena they might experience; all verbalizations were tape recorded. Each subject, wearing translucent goggles, lay on a comfortable bed in a small room. Except for the dark contour of the goggle frames, the visual field was diffuse, homogeneous, and of moderate intensity. Subjects also wore earphones carrying a constant "white noise" (a random mixture of many frequencies). The noise level was adjusted for each subject to mask ambient noises without becoming too disturbing or painful. Subjects were able to hear occasional airplanes overhead and slamming of doors. In general, normal visual and auditory stimulation was occluded and replaced with continuous *nonpatterned* stimulation. Heavy cotton gloves were worn to reduce tactile stimulation and cardboard cuffs placed on the forearms extended beyond the tips of the fingers. To reduce kinesthetic sensations and positional cues, subjects were instructed not to move about excessively and remained on the bed throughout the experiment. During the session, nobody entered the room or spoke with the subject.

2. *The "visual deprivation" or blackout group* (10 subjects) was treated in precisely the same fashion except that the translucent goggles were replaced by blackout goggles and the room was darkened.

3. *The "social isolation" or control group* (10 subjects) was treated in exactly the same way except that neither goggles nor earphones, gloves nor cuffs were used. This is a situation of relative social isolation, with vision, audition, and touch unimpaired, serving as a control.

Sequence of Procedure

All pre-test procedures were repeated after the experimental session to permit evaluation of changes.

1. *Psychiatric interview* a few days before the session.
2. *Psychologic tests* immediately before the session.
   a. Bender Motor-Gestalt Test.
   b. Visual perception tests involving discrimination of simple forms, size constancies, and optic illusions.
   c. Depth perception: Howard-Dohlman apparatus.
   d. Visual-motor coordination: pursuit rotor.
   e. Perceptual lag: specially designed apparatus.

3. *Eight-hour experimental session with:*
   a. Resistance (GSR) with plantar electrodes determined continuously for 15 minutes out of every half hour.
   b. EKG recorded intermittently.
   c. Behavioral observations regularly during session; tape recording of all vocalization.
4. *Repeat psychologic tests* immediately afterwards with retesting of perceptual functions as long as changes persisted.
5. *Clinical-type interview* immediately after testing.

Interviews both before and after were conducted along the lines of the associative anamnesis. All interviews were recorded for later analysis. Before the experiment, the focus was on motivation, expectations, anxiety, object relations, self concept, defenses, and visual imagery. Following the session, the interviewer tried to ascertain as completely as possible what actual thoughts, sensations, feelings, and fantasies had occurred. Because of the relatively unstructured nature of this situation, one might anticipate that a subject's expectations and his reactions to the experiment would show a relationship.

Description of Psychologic Tests

Administration of the test battery required approximately 40 minutes. The same sequence was always followed: pre-experimental (1) Bender, (2) depth perception, (3) perception of simple forms, (4) Müller-Lyer, (5) size constancy, (6) reversible figures, (7) pursuit rotor, (8) perceptual lag; postexperimental (1) perception of simple forms, (2) Müller-Lyer, (3) size constancy, (4) reversible figures, (5) perceptual lag, (6) depth perception, (7) Bender, (8) pursuit rotor. The order of testing was changed after the experiment to give what were thought to be the most sensitive tests first. This was done because perceptual effects are almost always transitory. The perceptual lag test, which was not used until this research was about half completed, was inserted 20 minutes after the termination of isolation.

1. *Bender Motor-Gestalt.* Subject was shown each card for 2 seconds and asked to make an accurate copy with pencil and paper. He was allowed to have as much time as required for each drawing. Drawings made before and after the session were compared with the originals and scored in relation to each other as "more," "less," or "equally" resembling the original.

2. *Depth perception.* The Howard-Dohlman apparatus was used with subject seated about 12 feet away. All trials were binocular, for 6 trials: 3 starting with the movable rod at the front and 3 with the movable rod at the rear of the apparatus. The subject was permitted to adjust the rod forwards and backwards until he was satisfied with its position. Subjects were scored for "greater" or "lesser" accuracy in the average setting of the rod on the post-test over the pre-test.

3. *Perception of simple forms.* Subjects were shown a straight line, a triangle, a cross, and 3 arrowheads at a distance of 12 feet. The figures were large, sharp, and clear, with good contrast; for example, the straight line measured 12½ by ½ inch. Level of illumination was 25 foot-candles. The subject was instructed: "I am going to show you some simple charts, and I should like to have you tell me what each one looks like to you—not what you think it really is, but what it looks like subjectively." If he reported significant perceptual distortion, he was asked to "make a drawing of the way this figure looks to you," and retested at 5-minute intervals until distortion was no longer recorded. A gross scoring system was devised based on the number and persistence of deviations from the original figure.

4. *Müller-Lyer.* Subject was shown an adjustable Müller-Lyer illusion and the effect was explained to him. In this test there are 2 horizontal lines of objectively equal length (approximately 7 and ¼ inches), but an illusion of disparity is produced by arrowheads at the ends of one line and tails at the ends of the other. The second line appears longer and has an adjustable segment at one end. The experimenter varied the position of the adjustable segment until the subject reported that the 2 horizontal lines looked equal to him.

5. *Size constancy.* Subject was presented at a distance of 12 feet with a chart containing 12 straight lines gradated from 11½ inches to 1 inch in length. He was asked 3 times to select from the chart a line equal in size to the line on a card held in his hand. The same procedure was repeated with a chart bearing 8 solid black circles graded from 3 inches to ¾ inch in diameter. The subject's score is the algebraic sum of the step deviations of his estimates from the true line or circle of equal size. Each line or circle in the graded series was counted as 1 step.

6. *Reversible figures.* Subject was shown in succession each of 2 ambiguous figures ("reversible blocks" and "two faces–vase" illusion; see figure 1). He was asked to fixate upon a point at the center of the figure for 60 seconds, telling the experimenter each time the figure changed. The score is the average time in seconds for each stabilization of the figure.

7. *Pursuit rotor.* Apparatus was a phonograph turntable rotating at 33⅓ rpm with a ⅜-inch contact spot at a radial distance of 4 inches. The subject was

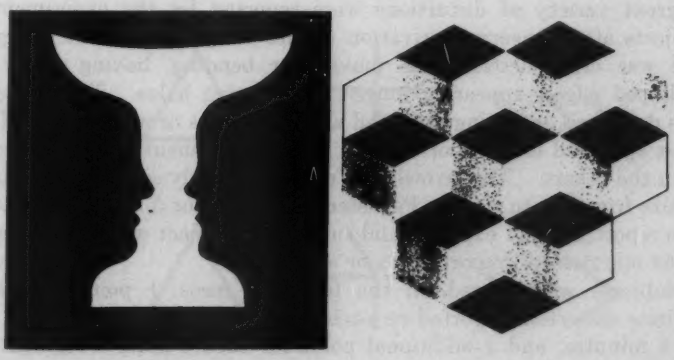


Figure 1. Reversible figures: two faces–vase (left) and reversible blocks.

handed an 8-inch stylus with a flexible tip and instructed to make contact as rapidly as possible on the signal. Starting position each time was with subject's hand resting on his knee. Before the pre-test, subject was given a number of practice trials. He then had 5 test trials. His score is the average time required to make contact.

8. *Perceptual lag.* Heron, Doane and Scott [4] had reported that after sensory deprivation, when a thin black line was rotated slowly against a dimly illuminated milk-glass screen in a darkened room, the line seemed S-shaped because the ends "lagged" behind the center part. This effect was reported by only 1 of the 3 subjects and was apparently not studied further. We used a special piece of apparatus to measure the apparent velocity of a moving contour (see Held and White [10]). Subject was seated at a table in a dimly lit room, with the apparatus at a distance of 3 feet from his eye. He fixated upon a ⅛-inch square black mark. A black sweep—6 inches long and ⅛-inch wide—rested in a horizontal position in the plane of the fixation mark. Subject depressed a microswitch. When the experimenter closed his switch, the horizontal sweep began to rotate counterclockwise at about 10 rpm, and an electric stopclock was activated. When the sweep reached the vertical (90°) position, it disappeared behind a white cover board. At 10° beyond the vertical (the 100° position) there was a fixed marker of the same size and shape as the sweep. Subject was instructed to release his switch, which stopped the clock, when he thought that the moving sweep was exactly underneath the stationary marker. He could not see the sweep moving through the last 10° but was forced to estimate its position in terms of his perception of its velocity.

Subjects were trained at this task until variability was reduced to a minimum and then given 20 test trials. Simple motor reaction time was controlled by measuring reaction to the flashing of a small red light built into the same apparatus.

PERCEPTUAL FINDINGS

Perception of Simple Forms

A great variety of distortions were reported by the experimental subjects after sensory deprivation (tables 2, 3; fig. 2). The straight line was often described as moving or bending, having wavy or scalloped edges, appearing longer, and having halos. The triangle was described as having extended angles or halos or as moving. The cross appeared to move or bend or have one segment darker or wider than the others. The arrowheads most frequently seemed to gradate in size from left to right. Persistence of effect for 5 minutes or more was reported by 11 experimental subjects; 1 subject who was retested at 64 minutes still reported major effects.

Subjects were scored on the following basis: 1 point for each definite distortion reported on each figure, 1 point for persistence up to 5 minutes, and 1 additional point for each 5-minute segment of the total persistence time, e.g., 2 points for 10 minutes, 3 points for 15 minutes. Scores for all 30 subjects were rank-ordered to permit

Table 2. ***Types of distortions of simple forms***

	Number of reports							
Subject group	*Larger*	*Smaller*	*Scalloped edges*	*Movement*	*Bending*	*Halo*	*Shimmering*	*Other*
Diffuse light	8	3	4	5	3	9	8	22
Blackout	4	3	3	4	4	3	1	7
Control*	5	0	1	2	1	2	0	3

*Of these 14 reports, 11 were made by 1 subject.

Table 3. ***Extent and persistence of distortions***

	Distortions reported (number of subjects)			
Subject group	*None*	*Minor*	*Major*	*Persist over 5 min*
Diffuse light	1	2	7	6
Blackout	3	1	6	5
Control	6	3	1	1

Minor = distortion score 2 or less.
Major = distortion score 3 or more.

statistical treatment. The Mann-Whitney U test was used to evaluate significance.

On this basis, "diffuse light" subjects reported significantly more perceptual distortions on the post-test than "blackout" subjects ($.025<P<.05$) and also significantly more than control subjects ($.001<P<.01$). Blackout subjects also reported significantly more distortions than control subjects ($.01<P<.02$). All these results are in the predicted direction. It should be noted that the effects reported were not bizarre or fantastic creations but seem rather

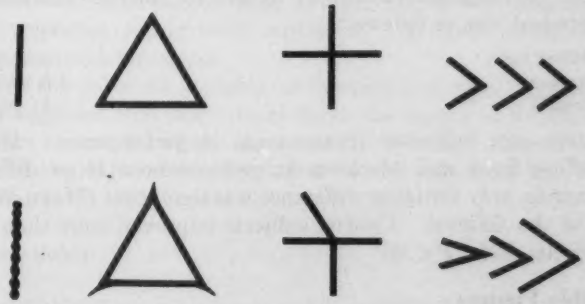


Figure 2. Typical distortions reported after 8 hours of sensory deprivation. Presented figure (above) and perceived figure.

natural or reasonable distortions of the presented figures. A number of subjects reported similar but far less extensive distortions on the pre-test, suggesting that these are the ways in which distortion would take place with such figures if the stabilizing effects of the normal perceptual process were weakened.

Bender Motor-Gestalt

The subject's net score was the number of post-test drawings judged as showing improvement over the pre-test in form quality minus the number of drawings showing poorer form quality. All 3 groups demonstrated improvement, as would be expected to result from practice. The mean net scores were:

Diffuse light	+1.4
Blackout	+1.1
Control	+2.5

Thus controls showed more improvement than either experimental group, but the only significant (Mann-Whitney U test) intergroup difference is that between blackout and control subjects ($.025<P<.05$) These results may well be more significant than the statistical tests would indicate, differences being masked by the deficiencies of the scoring method, which did not take into account differences in difficulty among drawings and varying degrees of improvement on individual drawings.

Pursuit Rotor

On the average, diffuse light and control subjects improved their mean times on the post-test, as would be expected from the effects of practice. Blackout subjects averaged slightly poorer times on the post-test. Average percent change in time for the post-test compared to the pre-test was as follows:

Diffuse light	−5.65%
Blackout	+0.96%
Control	−21.9%

A negative sign indicates improvement in performance. Although both diffuse light and blackout subjects showed large differences from controls, only the latter difference was significant (Mann-Whitney U test) at the .05 level. Control subjects improved more than blackout subjects, $.025<P<.05$.

Reversible Figures

Control subjects showed no significant changes in the rate of alternation of either of the 2 figures used. We had predicted that sensory

deprivation would result in more rapid alternation of ambiguous figures because of impaired stability of the perceptual process. With diffuse light subjects this seemed to be the case on the two faces–vase illusion. Six subjects reported a faster rate of alternation on the post-test, only 1 reporting slower alternation. Three subjects reported that they saw both alternatives simultaneously on both pre- and post-tests. The likelihood of such a result occurring by chance is only .062 (binomial test). With the reversible blocks, however, the result for diffuse light subjects was in the opposite direction: 8 subjects reported slower alternation on the post-test and only 1 reported faster alternation; 1 subject could not see the figure alternate on either pre- or post-tests. The probability of such a result occurring by chance would be only .02 (binomial test) if it were in the expected direction. According to a recent discussion by Goldfried[20] the true level of significance in this case is .06 because the result is in the unexpected direction.

If these results are valid, then tests with the 2 figures are simply not measuring the same effect. Phenomenologically, the 2 figures are different, and the spontaneous tendency to alternation was much greater for the two faces–vase figure, as indicated by the generally faster rates reported. Furthermore, most subjects had to be trained to see the 2 alternatives in the reversible blocks. There seemed to be a tendency to adopt one or the other alternative in the reversible blocks and fixate upon it, whereas with the two faces–vase the tendency was for more rapid alternation as the subject concentrated on the figure.

For blackout subjects there was no trend with reversible blocks, but results on the two faces–vase, although not statistically significant, paralleled those of diffuse light subjects. Five subjects reported faster post-test alternation, only 1 reporting slower alternation; 4 subjects reported seeing both aspects of the figure simultaneously on both pre- and post-tests.

Besides the inherent stability or instability of the 2 figures, some subjects reported that they could make the figures alternate at will and others accomplished the same end by blinking. It was not possible from the data collected to allow for the effects of this kind of influence.

Size Constancy

Results of this test are summarized in table 4. Although none of the intergroup differences are significant at the .05 level, the diffuse light subjects may show a trend in the same direction as that reported

by Heron, Doane, and Scott.[4] Diffuse light subjects tended to choose larger lines and circles in the post-test, whereas blackout and control subjects tended to choose smaller objects.

Table 4. ***Choice of larger or smaller objects on post-test for size constancy***

	Number of subjects		
	Larger	*Smaller*	*No change*
Diffuse light	6	3	1
Blackout	2	6	2
Control	2	6	2

Müller-Lyer Illusion

There were apparently no appreciable differences in amount of effect of this illusion.

Depth Perception

The results were no different from what one would expect from chance alone. The failure of this test to discriminate between subject groups may be due to the fact that it was not feasible to use the standard distance of 20 feet between subject and apparatus as prescribed by the designer of the test.

Perceptual Lag

Since work with this test was not begun until the present research was more than half completed, the number of subjects is too small to draw definite conclusions. These preliminary results, however, are worth noting because of parallel findings in another situation.

1. The apparatus and technique are suitable for studying the phenomenon of perceptual lag in sensory deprivation.
2. Simple motor reaction time was not significantly changed under diffuse light or blackout conditions.
3. Control subjects (3) showed no change in performance after the experimental session.
4. Blackout subjects (3) showed no change or perhaps a slight but insignificant speeding up of the sweep.
5. Diffuse light subjects (6) apparently saw the sweep moving more slowly than before the session. Differences between means for these individual subjects for 20 pre- and post-trials were significant (t test) at the .05 level or better.

These results, although based on a small N, parallel more extensive studies done at Brandeis University. Working only with vari-

ations in the visual field, Held and White [19] found that one-half hour's exposure to diffuse light and blackout conditions produced similar, though smaller, effects. These results lend additional support to the sensory deprivation findings and suggest that nonvisual aspects of sensory deprivation may be unnecessary for the production of perceptual lag.

Repeat Subjects

Four subjects were run in both of the 2 conditions: 3 with diffuse light first and 1 with blackout first. In general, results on the tests were similar for both sessions. On the perception of simple forms, each subject scored higher under diffuse light than under blackout conditions—results that are in line with other findings. This number of subjects, however, is too small for statistical significance.

Comment

Aside from any inadequacies of procedure, there are several reasons why many tests did not show significant results. A test may simply be inappropriate. The most likely reason, however, is that the effects are so evanescent, particularly after a sensory deprivation session of only 8 hours, that they cannot be picked up by these kinds of tests after the first few minutes, which are consumed with the first test. The order and timing of these tests are extremely important, and we deliberately used perception of simple forms first because in the pilot study it seemed the most sensitive test.

DISCUSSION OF PERCEPTUAL FINDINGS

What is perception? What is the process or function presumed to change in some way under conditions of sensory deprivation? For the purposes of the present discussion, we have adopted the following definition:

> Perception is a process by means of which the organism simplifies, stabilizes, and structures the environment in accordance with its needs and capacities.

Some effects described above may be interpreted in terms of a failure to stabilize the environment in the normal way. Accelerated rate of fluctuation with the ambiguous figure-ground illusion is the clearest example of this failure. We may also think of the reported distortions as tendencies to regress to a more primitive perceptual process because of weakened ability to impose structure on the perceptual environment.

Perhaps the reason the simple straight line is most often and most grossly distorted is that it has the least "thing quality" of all the forms presented; it is an abstraction. Organisms live and manipulate in a world of objects. Most perception is concerned with structuring what is perceived into recognizable objects; all types of constancies operate to hold objects stable and knowable, subservient to the needs of the organism. Therefore, it is likely that in this research effects were reported with abstract forms and not with familiar objects such as chairs, desks, or people, because, with these familiar objects, the complex variety of cues for "thingness" permits automatic and immediate correction for any distortion.

Besides being able to differentiate its environment into objects and to hold such objects constant under a variety of changes such as position and illumination, the mature organism has at its disposal an over-all spatial schema involving such attributes as up, down, right, left, and its own position in relation to other objects.

This over-all schema of spatial orientation may be conceptualized as a dynamic psychic structure that not only is continuously reaffirmed by interaction with the environment, but also is modified to accord with systematic changes in the environment; this activity may be called adaptation, accommodation, or reality testing. The spatial schema is closely related to bodily and social schemata, so that alteration of any one may produce changes in the others. All reported experiments with reduced environmental input, however, have drastically curtailed or modified cues for all 3 schemata, so that effects are hopelessly confounded.

The over-all spatial schema may be subdivided into lower-order schemata for vision, audition, and kinesthesis. Such schemata are not innate but have to be slowly and painfully learned by the infant organism. Riesen [21] has shown that interfering with this ontogenetic development by subjecting newborn monkeys to a deficient sensory environment for prolonged periods makes subsequent development of effective schemata extremely difficult and perhaps even impossible. Von Senden's review of the literature [22] on the vision of the congenitally blind given sight by surgical operation would seem to complement Riesen's findings. Such reports indicate that spatial orientation develops by repeated observation and testing of ordered relationships in the perceptual environment.

The perception of these environmental relationships is intermodal as well as intramodal; subschemata for different sense modalities are closely tied together and may themselves be used to reaffirm one another. For example, we see a cup of coffee, then reach out our hand to pick up the cup. Success in reaching and touching provides

kinesthetic and tactile confirmation of the visually "measured" position and distance of the cup.

The process of incorporating observed ordered relationships into a personal perceptual schema is one of extracting useful information from the welter of "noisy" sensations with which the organism is constantly bombarded. If the world of the infant is indeed a "blooming, buzzing confusion," as James has said, this is because the infant has not yet learned which of the incoming stimuli are meaningful and which are not. In order for sensory cues to acquire meaning and be incorporated into schemata, they must be regular, not changing capriciously or adventitiously.

The classic disarrangement experiment of Stratton,[23] the work of Kohler,[24] and current work by Held and his associates [25, 26] transform the visual environment of the subject by *systematically* shifting certain sets of cues. The new sensory field is, however, isomorphic with the old one, and furthermore, auditory and kinesthetic subschemata are not directly impaired. In an adult human's normal relation to the environment, "up" is always "up" and "down" is always "down." If he should wear inverting prisms, "up" becomes "down" and "down" becomes "up"; this reversed relation continues, thus becoming the basis for learning a whole new spatial order. Other relationships in the field are relatively undisturbed. Objects that had previously been contiguous, for example, remain so, and distances between familiar objects are not appreciably altered. The subject must modify his visual schema if he is in any way to function effectively with his new perceptual environment. He is able to do so by incorporating the new set of constant relationships that has been provided. Whether "up" is always "up" or is always "down" is relatively unimportant provided that the relationship is *continuous and predictable*. Man functions in a changing world by virtue of his ability to make predictions about relationships based on past experience with such relationships. But spatial orientation in the adult organism is contingent upon the integration of a complex assortment of visual, auditory, and kinesthetic cues. With one sensory modality occluded, the organism is still able to orient itself with the remaining senses. Experiments with rats trained to run in mazes demonstrated that even surgical interruption of 3 sense modalities did not prevent the animals from negotiating the maze.[27] The relationship between different modalities, however, is complicated, and it appears that the integration of motor output with visual input (feedback) is necessary for adaptation in the disarrangement experiments. In several recent studies, Held and his associates [25, 26] have demonstrated that active movement initiated by the subject is required for visual accommoda-

tion to prism-induced disarrangement. Subjects with 12° lateral displacement of the visual field accommodated rapidly when allowed to walk along a road, but did not accommodate when transported in a wheelchair over the same route.[25] Similar findings have been described with reference to hand-eye coordination when the apparent position of the hand was altered.[26]

Table 5. ***Reports of hallucinations under varying conditions of motility and vision*** **(*b*)**

Investigators	*Motility*	*Visual field*	*Hallucinations*
a. Wexler et al.[18]	Restricted	Monotonous, dim light	Yes
b. Heron et al.[4]	Restricted	Homogeneous, diffuse	Yes
c. Goldberger and Holt[7]	Restricted	Homogeneous, diffuse	Yes
d. Freedman and Greenblatt	i. Restricted	Homogeneous, diffuse	Yes
	ii. Restricted	Blackout	Yes
e. Cohen et al.[16]	Restricted	Blackout	Yes
f. Vernon et al.[13]	Free	Blackout	i. None ii. Minimal
g. Ruff and Levy[14]	Free	Blackout	Minimal

Crucial differences in motility and kinesthetic feedback may partially account for conflicting reports of the production of hallucinatory-like activity in "sensory deprivation" experiments, although in such experiments, variations in motility are easily confounded with variations in the visual field. Revising table 1 to include our own experiments may be helpful (table 5).

In every instance of restricted motility (a, b, c, d, e), hallucinations have been reported, whereas in 2 experimental situations with free motility (f, g), minimal or no hallucinations were reported. In fact, the conditions of these experiments (f, g) were such that subjects were forced to orient themselves by moving about. Unfortunately, there are many other differences—besides motility and visual field—between these various experimental situations, so that comparisons must be highly tentative. Nonetheless, in 2 experimental situations (d-ii, e) where motility was restricted under blackout conditions, hallucinations were still reported. These data would seem to provide further evidence for the integrative nature of spatial and cognitive orientation. Now it is important that studies be made varying motility in combination with different visual and auditory conditions

in order to throw more light on the nature and conditions of integration. It appears likely that although some one sensory occlusion may be necessary to produce "sensory deprivation" effects, the sufficient condition will prove to be a combination of different atypical sensory conditions.

When the world no longer changes in an orderly fashion, it fails to provide reliable cues. If, with reduced external stimulation, a person is presented with a perceptual environment containing no orderly relationships, his previously learned spatial schema becomes useless. What is worse, it becomes impossible to modify the old schema or develop a new one since he cannot extract from non-order the information required to maintain any spatial schema at all. Since spatial orientation is essential to survival, he attempts to accommodate to the "noise," seeking order and meaning where there is none. This futile attempt to fit a previously learned schema to the new perceptual environment results only in a degradation of the perceptual frame of reference.

It is always prudent to remember that the brain, at least in higher forms, is more than a glorified computer passively accepting and analyzing external inputs. To a considerable extent, the brain provides inputs of its own, is self stimulating. We have compared the effects of continuous exposure to strong diffuse light with blackout conditions. The spatial schema is apparently degraded in either situation despite the obvious differences in quality and sheer quantity of stimulation. If the inactive brain were simply a biologic motor idling in neutral, there would be no reason to expect changes with blackout conditions. We are forced to consider the conative aspect of the situation. The fact that changes occur with both diffuse light and blackout indicates that it is the absence of order or meaning rather than the specific nature of the stimulus field that tends to degrade perceptual organization. We must, therefore, think in terms of an active process in the waking state that strives or seeks continuously and automatically to find ordered relationships in the perceptual environment.

We would postulate that it is this process of seeking order where there is no order and of attempting to incorporate non-order into previously existing schemata that accounts for the perceptual changes, instabilities, and inconstancies described in the McGill studies [4] and in our own studies. The properly functioning organism imposes structure on a fluid environment according to a learned set of relationships that have proved dependable and useful. Such a structure is not necessarily the same for various forms of life but must be related to the needs of the organism and sufficiently congruent with important

aspects of the external world to afford satisfaction of those needs.[28] Perception is thus always selective and is always testing the cues that are essential to the maintenance of the various schemata. With the breakdown of the internal frame of reference, it becomes increasingly difficult and in fact impossible to structure the environment, to impose constancies and stabilities on the perceived natural world. As a result, contours fluctuate, ambiguous figures alternate rapidly, and simple geometric figures change their size and shape. Our data suggest that these effects may be due to the release of tendencies inherent in the primitive perceptual process but normally held in check by a process of structuring and stabilizing the visual field.

(Part II of this article will appear in the December issue. All references will be found at the end of the second part.)

DENATURED LANGUAGE, HARD READING

In the rush to publish, padding and jargon are often employed to make up for a paucity of content. Inadequate attention is given to the meaning of words, and the influence of careless speech in daily life casts a long shadow on much scientific and technical writing. This does not mean that technical terms should not be used. On the contrary, there is a legitimate use for a specialized vocabulary that can be employed for precise and economical communication by experts in a given field. This is one reason for the use of mathematical language in certain branches of science. The fact is that technical terminology is like all language in that most words have several meanings or shades of meaning, that these tend to change in the course of time, and that new words or old words with new meanings are bound to come on the scene. Any editor must learn to accept this fact of life. At the same time, such recognition cannot be used to excuse sloppy writing that results from fuzzy thinking, or from the employment of denatured language acquired from textbooks and learned treatises, or from a combination of these factors. The editors must endeavor to offset the corrupting effects of such influences, for as Sheridan stated so succinctly and forcibly: "Easy writing's vile hard reading."—GEORGE ROSEN: Editorial Viewpoints. *International Record of Medicine*, July 1960.

Use of a Porous Synthetic Sponge (Ivalon) in Surgery I. Tissue Responses After Implantation

RICHARD H. ADLER, M.D.
CLEMENT DARBY, M.D.

IN THIS NEW ERA OF SYNTHETIC MATERIALS—the so-called plastics—new avenues have opened for their clinical applications in the field of surgery. Of the various synthetic substances, probably none has been used as widely, with as many diverse surgical applications, as has Ivalon, a sponge of formalinized polyvinyl alcohol. This has occurred during the past 10 years, following the introduction of Ivalon in 1949 as a plombage after pneumonectomy in dogs.[1]

During this decade, Ivalon has been used for nearly every conceivable surgical application: for reinforcing various types of hernias and tissue defects in the abdomen, pelvis, diaphragm, and chest wall;[2-9] for partial or complete replacement of trachea, bronchi, and esophagus;[10-12] for ureters;[13] for bile ducts;[14] in an artificial heart-lung preparation;[15] as a prosthesis for filling an empty intrathoracic space and as plombage in compressing diseased lung;[16-20] as a stimulant for myocardial revascularization;[21] in cardiac surgery to bridge septal defects, to widen stenosed vessels, to support incompetent valves, and to function as new valve leaflets;[22-29] in vascular surgery as a bypass shunt, as an external vascular support, and as arterial and venous prostheses in vessels ranging in size from the aorta to the coronary artery;[30-66] as a hemostatic agent for liver and kidney wounds;[67] in plastic surgery for various types of molds and subcutaneous implants;[68-73] in orthopedic surgery as a scaffold for new bone growth;[64, 74-78] in neurosurgery for replacing the dura;[79] and in

From Buffalo General Hospital and the Department of Surgery, University of Buffalo School of Medicine, Buffalo, N.Y. Supported by the Research and Development Division, Office of the Surgeon General, Department of the Army, under Contract No. DA-49-007-MD-750.

562174 O—60——8

various types of ophthalmologic surgery.[80–83] A variety of additional studies on Ivalon have been reported.[84–90] Although not complete, this listing attests to the versatility and widespread use of Ivalon.

We too have been impressed with certain desirable features of Ivalon, such as its porosity, compressibility, ease of handling, and ability to hold sutures. Our early laboratory experience with Ivalon implanted in animals made us aware of rather marked changes that took place after in vivo implantation. Attractive in vitro properties were greatly altered after a sufficient period of animal implantation.

A review of the literature showed a disturbing difference of opinion concerning the value of Ivalon despite its widespread use in clinical surgery. Indeed, it is surprising to observe the extent to which the material has been used in clinical surgery often with little experimental evidence to substantiate such ready application in man. With few exceptions, little effort has been made to quantitate and control its fabrication and to study the ultimate disposition of the prosthesis in the body in relation to its initial physical properties. It seemed to us that poorly controlled fabrication of Ivalon prostheses might in part explain the greatly conflicting opinions concerning the worth of this material in clinical surgery. There appeared to be a need to study certain basic properties of Ivalon and the effects of carefully controlled fabrication upon those properties before and after implantation in the body. We reasoned, for example, that haphazard fabrication of an Ivalon tube for use as an arterial prosthesis might explain why one investigator would report excellent results, whereas another would find dilatation and rupture.

The present study was undertaken, in part, to help resolve some of these unsettled issues. The data to be reported are divided into 2 parts. The first part is concerned with gross and histologic studies of Ivalon implants subjected to accurate ratios of compression and the tissue response to these implants. The second part* deals with the effects of fabrication upon certain properties of Ivalon, in particular tensile strength and solubility; some practical considerations based upon our experiences with Ivalon will also be presented in this part.

MATERIALS AND METHODS

Ivalon is a high polymer produced by the formalinization of polyvinyl alcohol. Before the material has reached the final degree of polymerization, air is blown through the liquid plastic. At the completion

*Part II of this study will appear in the December issue of the *Journal*.

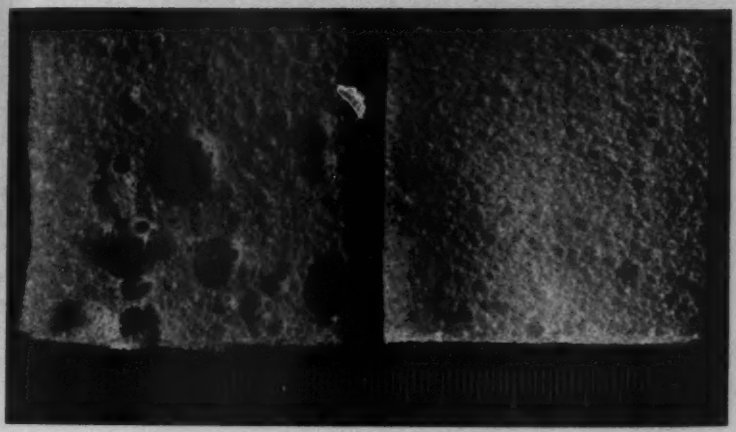


Figure 1. Close-up of small squares of Ivalon. Commercially available surgical grade Ivalon (*left*). Finer, more uniformly porous newer Ivalon (*right*).

of the polymerization, a solid form is obtained, which when moist is supple, hygroscopic, and quite easily compressed. When allowed to dry, the sponge becomes firm and rigid; in this form it is easily cut into various shapes. The commercially available surgical grade Ivalon is sealed within polythene bags to keep the sponge soft and supple. It is white, odorless, tasteless, with an appearance on cross section that has been likened to a slice of bread.

Moistened surgical grade Ivalon sponge can be readily compressed up to ratios of about 16:1. Since the sponge is a thermoplastic resin, if it is compressed and heated above 95° C and then allowed to cool to room temperature, it will maintain the shape in which it was compressed. The sponge contains a "shape memory"; if reheated to above 95° C without restraints to maintain its compressed shape, it will return to its original uncompressed dimensions.

Two types of Ivalon sponge were used in this study. They differed only in the size and uniformity of their porosity. During the early part of the work, the standard commercially available surgical grade Ivalon was used. This sponge has moderate porosity, with occasional large defects of aeration or "blow holes," which occur where the foaming process was not uniform (fig. 1). Such defects will of course affect the strength of the sponge cross section containing the "blow hole." Later in the study a newer sponge with fewer and smaller "blow holes" and with finer and more uniform interstices was utilized (fig. 1).

Before use, the sponge block was washed overnight in running tap water to remove any impurities. It was then allowed to air dry slowly for several days, producing a firm block that was readily sliced into sheets of any desired thickness, and cut into sheets on a circular meat slicer. In this study, the sliced sheets of sponge were compressed between 2 sheets of plywood-reinforced plate glass to a final thickness of either 1 or 2 mm. The final thickness was easily controlled by using shims of glass microslides between 2 pieces of plate glass, 1 slide for a final thickness of 1 mm and 2 slides for a final thickness of 2 mm. C-clamps were applied outside the plywood–glass plate sheets to maintain the compression. The entire clamp jig was then placed in an autoclave and exposed to live steam at 1 atmosphere pressure, 100°C for one-half hour. The jig was then allowed to cool to room temperature with the clamps in place. The cooled Ivalon retained its compressed shape once the clamps were removed.

For the commercially available surgical grade Ivalon, pieces were produced with a final thickness of 1 and 2 mm and compression ratios of 1:1, 2:1, 4:1, 8:1, and 16:1. The newer Ivalon with more uniform porosity was also produced in thicknesses of 1 and 2 mm, with compression ratios of 1:1, 2:1, 4:1, and 6:1. Higher compression ratios were not studied with the latter material, since it appeared that higher compression ratios produced an almost impermeable sheet.

For histologic study, pieces measuring 1 inch by 1 inch from each compression and from each thickness were sterilized by immersion in 1:1,000 benzalkonium (Zephiran) chloride solution for 24 hours. A limited number of pieces measuring 1¼ by 4¼ inches by 1 or 2 mm in thickness were similarly prepared for implantation, to be used for tensile strength testing as well as histologic study. This attempt to obtain in vivo tensile testing specimens was shortly abandoned for reasons to be discussed.

Under aseptic conditions, the sterilized Ivalon specimens were implanted subcutaneously on the abdomen and flank of rabbits. The pieces were held in position by a suture in each corner. Postoperatively the animals received penicillin and streptomycin daily for 5 days. Four groups of rabbits were used for implanting the 1-inch square specimens: 2 series of standard Ivalon and 2 of the finer Ivalon. For each of the 2 grades of Ivalon, a 1-mm and a 2-mm thick series with increasing degrees of compression were implanted. The animals were sacrificed according to protocol at intervals through 1 week; then at 2, 4, 8, 16, and 32 weeks and finally at 1 year. Specimens with infection were excluded and replaced by specimens from another rabbit. At autopsy, the gross appearance of the sponge and

surrounding tissue was noted and the sponge then prepared for histologic study. In this way a complete spectrum of Ivalon of 2 grades, 2 initial thicknesses, and increasing but controlled compression ratios was obtained for periods up to 1 year.

RESULTS

Our original attempts to combine histologic and tensile strength studies by implanting large pieces of Ivalon subcutaneously in rabbits were abandoned for several reasons. The areas of undermined skin with the larger Ivalon implants tended to collect large pockets of serum, which the rabbits scratched or bit open, with resultant secondary infection. The abscesses and draining sinuses usually persisted until the Ivalon implant sloughed out or was removed surgically. It soon became evident, in cases where infection did not occur, that uncontrollable adherence of the fibrous capsule and infiltration of the sponge with fibrous tissue would prevent accurate measure of the tensile strength of the sponge alone. This will receive further comment in part II of this study. A careful 2-layer closure of skin and subcutaneous tissues resulted in an incidence of infection of only 3 percent (3 per 100 implants) in the 1-inch square specimens.

Gross and Microscopic Studies

After review of all data, a rather definite and predictable pattern of tissue response to the implanted sponge became evident. As might be expected, the pattern of tissue response was considerably delayed in the sponge implants with the greatest compression and thickness as compared with the thinner implants with low compression. Nevertheless, in even the thickest, most compressed sponge, the pattern of tissue response could usually be seen to complete itself if the sponge was left in the body long enough.

The initial response to the implanted Ivalon was a filling of the sponge interstices with a serous fluid that had an appearance similar to edema fluid (fig. 2A). This stage was seen within a few days in most groups, but was still evident 1 week after implantation in the 2-mm thick sponges with the highest compression ratios. Following this phase, the sponge interstices became filled with inflammatory cells—primarily round cells, polymorphonuclear cells, and eosinophils (fig. 2B). Only the faint beginnings of a fibrous capsule surrounding the surface of the sponge could be detected histologically at this time. In the next phase, a rather distinct fibrous capsule could be seen

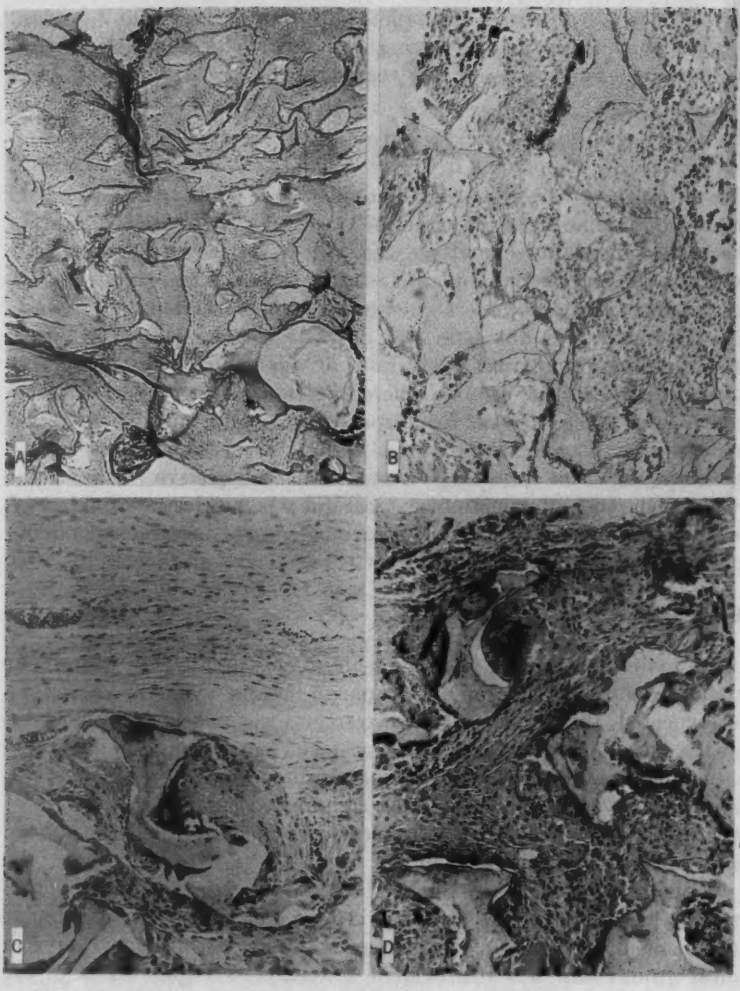


Figure 2. Photomicrographs of Ivalon sponge 1 mm thick, compression ratio 4:1, after implantation in rabbits for varying time intervals. (A) 1 week: fluid filling sponge interstices; (B) 2 weeks: cellular infiltration of interstices; (C) 4 weeks: early fibrous encapsulation and fibrovascular infiltration of sponge; (D) 16 weeks: organized fibrous infiltration, with foreign body giant cells in sponge interstices. (x 100, reduced about one half.)

surrounding the entire section of the sponge. The capsule was composed of mature collagen fibers and fibrocytes oriented parallel to the flat surface of the sponge section (fig. 2C). The capsule also extended around the edges of the implant. When pieces were removed from the animal at this stage, the fibrous capsule was distinct on gross inspection. It might adhere firmly to the surface of the sponge or it might easily be stripped free. Histologically there did not appear to be any marked infiltration of fibrous tissue into the sponge interstices, although the cellular infiltration at this time was not nearly as pronounced as in the earlier stages.

Generally, as the external fibrous capsule became thicker and better defined, the sponge interstices showed evidence of invasion with fibroblasts and macrophages. Until this stage was reached, foreign body giant cells were rarely seen in the sponge interstices, although a few giant cells could be seen along the inner surface of the fibrous capsule. From this point on, fibrous tissue proliferation was active within the sponge, and the interstices became filled with mature fibrous tissue and many small capillaries. Multinucleated giant cells were now conspicuous in the sponge and along the fibrous capsule (fig. 2D). It should be noted that the foreign body giant cells were seen in the sponge interstices but not in the surrounding tissues outside the fibrous capsule. At this time a very distinct capsule, which could be seen grossly, could be removed from the sponge only by sharp dissection.

The sequence of events as described, from early fluid and cellular infiltration to final fibrovascular invasion and encapsulation, was usually complete in about 4 weeks for both grades of Ivalon and in both thicknesses of sponge with compression ratios of 1:1 and 2:1. It took approximately 8 weeks to complete the sequence in the 4:1 compression of the commercial grade Ivalon and in the 4:1 and 6:1 compression of the finer grade Ivalon. The 8:1 and 16:1 compression of the commercial sponge appeared to take somewhat longer, although grossly the fibrous capsule was evident and adherent after about 8 weeks of implantation.

The desirable properties of pliability and elasticity were lost to variable degrees with progressively longer periods of in vivo implantation. This also varied with the degree of compression: from 1:1 (no compression) to 16:1 (high compression). The uncompressed implant had a less pronounced fibrous capsule and more fibrovascular infiltration, and in time frequently appeared to lose its continuity and show evidence of fragmentation with dissolution. By contrast, the highly compressed implant exhibited a thick white fibrous capsule, with variable degrees of adherence to the sponge, less fibrovascular

infiltration, and loss of porosity, becoming rigid, wrinkled, and shrunken from contraction of the fibrous capsule. At less extreme compressions, the implants generally exhibited increasing stiffness and loss of pliability with time. The degree of wrinkling and shrinkage varied directly with the thickness of the fibrous capsule and inversely with the amount of fibrovascular infiltration. Elastic fibers were not noted in the sponge interstices.

DISCUSSION

Most reports mention relatively mild foreign body reaction to implanted Ivalon, and in some short-term studies it is stated that absolutely no reaction has been observed. As a result, some authors have referred to Ivalon as an "inert" material. In our study, only minimal inflammatory reaction was noted outside the capsule that formed around the sponge. In the tissue invading the sponge interstices, however, a fairly marked reaction was observed, especially if the sponge had been in place for over 4 weeks. In some respects this initial reaction resembled the histologic sequence following trauma.

Ivalon cannot be considered inert. It has the property of wettability, which is undesirable from the standpoint of exciting tissue reaction and inviting chemical degradation. The sponge stimulates more response than do loosely fabricated meshes of plastics such as Teflon or Dacron.[91, 92]

A definite pattern of tissue response could be seen within the interstices of the sponge, from initial fluid and inflammatory cellular infiltration to eventual fibrovascular proliferation. When this finally resulted in avascular fibrosis, the desirable physical properties of the sponge were lost. Of interest were the foreign body giant cells noted within the interstices of nearly all implants after 8 weeks. This reaction was always noted initially at the inside edge of the fibrous capsule that formed around the sponge implant.

Consideration of the properties of an ideal material for use as a substitute for living tissue suggests that the potential carcinogenic effects of implanted material cannot be overlooked. Since Ivalon is a high polymer belonging to the so-called macromolecules, a group shown to have definite carcinogenic effects,[93–95] this matter deserves consideration. It is beyond the scope of this article to review studies of the carcinogenicity of plastics other than to say that most of these materials, Ivalon as well as Nylon, Dacron, and others, have been shown to have definite carcinogenic effects when implanted in certain

experimental animals. It would appear that the physical form of the plastic insert was as important as its chemical nature in determining its tumor-producing potential. Oppenheimer and associates [93–95] noted a high incidence of fibrosarcomas in animals with implants of impermeable films; yet little or no carcinogenic effect was observed from the same plastics implanted as fabrics or perforated films. Ivalon sponge appeared to cause relatively few tumors when compared with implants of impermeable films. It should be noted, however, that in our greatest compression ratios, following in vivo implantation, the physical characteristics of Ivalon approached those of an impermeable film.

The studies of Oppenheimer and associates [93–95] also showed that tumor incidence was highest in those implants in which a thick, well-oriented layer of fibrous tissue developed parallel to the flat surface of the implanted material. Furthermore, the initial evidences of sarcoma formation were noted at the inside edge of the thick fibrous layer, against the flat surface of the plastic implant. It is interesting to note that in our histologic studies the initial formation of foreign-body giant cells was observed at the inside edge of the well-oriented fibrous capsule surrounding the compressed sponges. This region would appear to have the highest potential for inflammatory reaction and malignant transformation. After 6 months this potential in the fibrous capsule is still present even if the implanted material is removed.

To our knowledge there have been no reports of tumor formation in human beings despite the many clinical implants of Ivalon. Nevertheless, the possiblity of future tumor formation in man, especially with highly compressed implants, must await the test of time before carcinogenic activity can be definitely excluded. For moderate compressions, where fibrovascular ingrowth is fairly rapid and a thick capsule is not so readily formed, the occurrence of neoplasm from Ivalon should theoretically be less likely.

It is unfortunate that the desirable features of pliability and elasticity that can be demonstrated so nicely before implantation are lost following prolonged residence in the animal body. We have particularly noticed this loss with tubular Ivalon prostheses used as thoracic aorta grafts. With higher compression to increase tensile strength as well as to reduce blood leakage, there was increased fibrous encapsulation with less fibrovascular infiltration. The fibrous bridge across the anastomosis between host aorta and a highly compressed Ivalon arterial graft was less secure. Also, the pulsatile elasticity noted in the Ivalon aortic graft at the time of implantation had disappeared when examined at a later date.

Uncompressed molds such as those used for breast implants or intrathoracic plombage will lose their initial light fluffiness as fluid and cells permeate the interstices of the sponge. In time there will be a loss in volume or shrinkage as fibrovascular tissue organizes in the sponge matrix. When this is finally replaced by a largely avascular type of fibrous tissue, the implant will assume a shrunken hard form that will be especially objectionable for subcutaneous implants.

Uncompressed sheets of Ivalon sponge show a tendency toward fragmentation and dissolution. In this form it would have little value as a supporting prosthesis. When highly compressed, it assumes many of the undesirable features of solid nonporous materials and films. The resultant loss of fibrovascular infiltration may interfere with the proper formation of a neointima in Ivalon blood vessel grafts. The loss of fibrovascular infiltration will also prevent intimate incorporation of the sponge with adjacent tissues. In fact, a highly compressed sponge implant not uncommonly lies free or only partially adherent to the thick almost cartilage-like surrounding fibrous capsule. The shrinkage, wrinkling, and rigidity that we have seen with highly compressed sheets of Ivalon used for replacing defects in thoracic and abdominal wall in animals are undesirable.

That Ivalon implants are not tolerated in the presence of infection is a serious practical disadvantage. We have found that infection almost always persists, and the Ivalon implant lies free in an abscess cavity until it is removed or extruded. By contrast, we have observed that a widely porous mesh of plastic fibers not only functions better as a supporting prosthesis for certain types of hernias and tissue defects, but does not exhibit this degree of rejection in the presence of an infection.[96] Compared with such a mesh, Ivalon sponge adds much more foreign substance with less porosity per unit area.

We have also been disappointed with the use of Ivalon in other forms of tubular prostheses. In the esophagus, stenosis usually followed in time as the fibrous tissue contracted. In the trachea, we have incorporated leucite rings and metallic coils to maintain shape, but the Ivalon prostheses eventually failed.

There remains an unanswered need for a spongelike prosthesis, particularly in certain types of plastic and reconstructive surgery. This demand has not been met by solid or fabric forms of plastics. We have initiated some experiments with some "self-foaming" types of polyurethane sponges, in which the air holes do not intercommunicate as they do in Ivalon. Theoretically, one would hope that such a sponge would allow superficial fibrovascular infiltration for incorporation with adjacent tissues but would prevent deeper fibrous pene-

tration. Whether a sponge of this type will maintain desirable properties when used as a mold or space filler in the body will have to await further study.

We have had no occasion to use Ivalon in man, but from our laboratory experience we must conclude that Ivalon has not lived up to the early burst of enthusiasm expressed for it. Newer synthetic materials seem to offer more promise for most of the applications earlier envisioned for Ivalon.

SUMMARY

Most of the easily demonstrated desirable features of Ivalon sponge are altered following implantation in the animal body. The in vivo response varies considerably as the ratio of carefully controlled sponge compression increases. Uncompressed sponge can be seen to fragment and partially dissolve. By contrast, highly compressed sponge specimens lose porosity, have less fibrovascular infiltration, and become surrounded by a thick fibrous capsule. Pliability and elasticity decrease as fibrous encapsulation and infiltration of the sponge progress. Wrinkling, shrinkage, and firmness will follow in time, depending upon the form of the implanted sponge and the extent and distribution of the avascular fibrous tissue.

Ivalon is poorly tolerated in the body in the presence of infection—a serious drawback. Tissue response, especially to highly compressed Ivalon, suggests that its carcinogenic potential cannot be excluded at this time. The malignant potential of implanted Ivalon is discussed.

Ivalon sponge would appear to have very limited value in clinical surgery today. A number of the newer synthetic materials may fulfil certain surgical needs in a more satisfactory manner. Some future modifications of a spongelike prosthesis may prove to be more suitable in certain specialized areas of surgery.

REFERENCES

1. Grindlay, J. H. and Clagett, O. T.: Plastic sponge prosthesis for use after pneumonectomy. *Proc. Staff Meet. Mayo Clin.* 24: 538–539, Oct. 12, 1949.
2. Abrahams, J. I. and Janassen, O. T.: Use of polyvinyl sponge in repair of abdominal wall hernias. *Surgery* 42: 336–341, Aug. 1957.
3. Cooley, J. C., Grindlay, J. H. and Clagett, O. T.: Esophageal hiatal hernia; anatomic and surgical concepts, with special reference to use of Ivalon prosthesis in repair. *Surgery* 41: 714–722, May 1957.
4. Fitch, E. A. and Fries, J. G.: Ivalon as chest wall prosthesis; 18-month follow-up. *J. Thoracic Surg.* 36: 262–267, Aug. 1958.

5. Fitch, E. A., Glass, H. G. and Aves, F. H.: Ivalon as chest wall prosthesis. *J. Thoracic Surg.* 34: 265–268, Aug. 1957.
6. Schofield, T. L., Hollenbeck, G. A., Grindlay, J. H. and Baldes, E. J.: Use of polyvinyl sponge in repair of experimentally produced defects in abdominal wall. *A.M.A. Arch. Surg.* 68: 191–207, Feb. 1954.
7. Pesek, I. G. and Keeley, J. L.: Polyvinyl formalinized (Ivalon) sponge in repair of diaphragmatic hernia. *A.M.A. Arch. Surg.* 77: 18–21, July 1958.
8. Pesek, I. G., Schairer, A. E. and Keeley, J. L.: Repair of defects in diaphragm of dogs using sheets of Ivalon sponge and fresh homologous grafts of fascia lata, in American College of Surgeons: *Surgical Forum*, No. 7. W. B. Saunders Co., Philadelphia, Pa., 1957, pp. 178–181.
9. Schofield, T. L.: Polyvinyl alcohol sponge; inert plastic for use as prosthesis in repair of large hernias. *Brit. J. Surg.* 42: 618–621, May 1955.
10. Björk, V. O. and Rodriguez, L. E.: Reconstruction of trachea and its bifurcation; an experimental study. *J. Thoracic Surgery.* 35: 596–603, May 1958.
11. De La Fuente, D. A.: El Ivalón en la cirurgia plastica del esófago torácico. *An. Acad. nac. méd. Madrid.* 73: 279–305, 1956.
12. Jesseph, J. E., Stevenson, J. K., Harkins, H. N. and Merendino, K. A.: Human measurements involved in tracheobronchial resection; reconstruction and prosthetic replacement; a preliminary report on Ivalon sponge, in American College of Surgeons: *Surgical Forum*, No. 7. W. B. Saunders Co., Philadelphia, Pa., 1956, pp. 218–221.
13. Ulm, A. H. and Lo, M. C.: Total bilateral polyvinyl ureteral substitutes in dog. *Surgery* 45: 313–320, Feb. 1959.
14. ReMine, W. H. and Grindlay, J. H.: Skin-lined omentum and plastic sponge tubes for experimental choledochoduodenostomy. *A.M.A. Arch. Surg.* 69: 255–262, Aug. 1954.
15. Heupel, H. W. and Wild, J.: Design of artificial lung using polyvinyl formal sponge. *Lancet* 271: 1246–1247, Dec. 15, 1956.
16. Allen, M. B., Jr., and Webb, W. R.: Use of plastic sponge (Ivalon) in operative procedures for pulmonary tuberculosis. *J. Thoracic Surg.* 34: 21–35, July 1957.
17. Bridge, E. V., Allen, G. S., Ellis, F. H., Jr., and Clagett, O. T.: Complications associated with polyvinyl sponge prostheses and plombage in surgical management of pulmonary diseases. *Am. Rev. Tuberc.* 74: 581–589, Oct. 1956.
18. Dailey, J. E.: Ivalon sponge plombage. *Am. Rev. Tuberc.* 78: 478–484, Sept. 1958.
19. Gale, J. W., Curreri, A. R., Young, W. P. and Dickie, H. A.: Plastic sponge prosthesis following resection in pulmonary tuberculosis. *J. Thoracic Surg.* 24: 587–610, Dec. 1952.
20. Hurst, A., Grow, J. B., Levine, S. and Perlmutter, H. M.: Use of plastic sponge in surgical treatment of pulmonary tuberculosis (Prel. Report). *Dis. Chest* 20: 134–138, Aug. 1951.
21. Smith, F. R. and others: Myocardial revascularization by means of cardiopneumopexy and Ivalon graft. *Dis. Chest* 33: 533–535, May 1958.
22. Bahnson, H. T. and Baker, C. B.: Study of prosthetic materials used inside the heart, in American College of Surgeons: *Surgical Forum*, No. 4. W. B. Saunders Co., Philadelphia, Pa., 1953, pp. 78–87.

23. Conklin, W. S., Maurice, G. L. and Bergquist, S. F.: Mitral valve surgery: Transventricular valvuloplasty and use of Ivalon sponge pack for mitral insufficiency. *Dis. Chest* 35: 291–301, March 1959.
24. Donald, D. E., Kirklin, J. W. and Grindlay, J. H.: Use of polyvinyl sponge plugs in closure of large atrial septal defects created experimentally. *Proc. Staff Meet. Mayo Clin.* 28: 288–295, May 20, 1953.
25. Ellis, F. H., Jr., and others: Diagnosis and surgical treatment of common atrium (cor triloculare-biventriculare). *Surgery* 45: 160–172, Jan. 1959.
26. Johns, T. N. P. and Blalock, A.: Mitral insufficiency; experimental use of mobile polyvinyl sponge prosthesis. *Ann. Surg.* 140: 335–341, Sept. 1954.
27. Kirklin, J. W. and others: Surgical treatment for tetralogy of Fallot by open intracardiac repair. *J. Thoracic Surg.* 37: 22–51, Jan. 1959.
28. Lewis, F. J. and Taufic, M.: Repair of experimental interventricular septal defects during hypothermia with molded polyvinyl sponge. *Surg. Gynec. & Obst.* 100: 583–590, May 1955.
29. Rumel, W. R. and Cutler, P. R.: Correction of mitral insufficiency with transvalvular polyvinyl formalinized plastic (Ivalon) sponge prosthesis; a preliminary report. *Dis. Chest* 33: 401–413, April 1958.
30. Ayers, W. B., Cincotti, J. J. and Gliedman, M. L.: Experiences with Ivalon (polyvinyl formalinized) sponge prostheses for vascular replacements. *A.M.A. Arch. Surg.* 74: 173–180, Feb. 1957.
31. Brown, L. and Essig, H.: Fatal rupture of Ivalon (polyvinyl formalinized) sponge aortic graft into duodenum; case report. *A.M.A. Arch. Surg.* 79: 72–74, July 1959.
32. Cockett, F. B. and Norman, A. G.: Late results of direct surgery of aortic bifurcation and its major branches. *Brit. M. J.* 1: 727–734, March 29, 1958.
33. Cole, W. R., Helmsworth, J. A. and Herrmann, L. G.: Ivalon tubes for by-pass of long segments of aorta. (Abstract) *Circulation* 14: 919–920, Nov. 1956.
34. Conklin, W. S., Grismer, J. T. and Aalpoel, J. A.: Resection of aortic arch. *Ann. Surg.* 148: 226–229, Aug. 1958.
35. Crawford, E. S., DeBakey, M. E. and Cooley, D. A.: Clinical use of synthetic arterial substitutes in 317 patients. *A.M.A. Arch. Surg.* 76: 261–270, Feb. 1958.
36. Creech, O., Jr., DeBakey, M. E. and Mahaffey, D. E.: Total resection of aortic arch. *Surgery* 40: 817–830, Nov. 1956.
37. DeBakey, M. E., Creech, O., Jr., and Morris, G. C., Jr.: Aneurysm of thoracoabdominal aorta involving celiac, superior mesenteric and renal arteries; report of 4 cases all treated by resection and homograft replacement. *Ann. Surg.* 144: 549–573, Oct. 1956.
38. Denman, F. R. and Fitch, E. A.: Arterial grafts; compressed molded Ivalon tubes. *J. Internat. Coll. Surg.* 27: 335–341, March 1957.
39. Deterling, R. A.: Editorial. *Surg. Gynec. & Obst.* 104: 227–232, Feb. 1957.
40. Eiken, O., Wulff, H. B. and Hallen, L.: Plastic material in experimental vascular surgery. *Acta chir. scandinav.* 114: 75, Jan. 31, 1958.
41. *Ellis, F. H., Jr.*, and Kirklin, J. W.: Aneurysm and thrombotic occlusion of abdominal aorta. *Postgrad. Med.* 20: 494–500, Nov. 1956.
42. Flom, R. S. and others: Atherosclerotic changes in grafts of thoracic aorta. *Surgery* 44: 356–360, Aug. 1958.
43. Goetz, R. H.: Polyvinyl sponge for aortic grafts. *South African Med. J.* 31: 582–586, June 1957.

44. HARRISON, J. H.: Ivalon sponge (polyvinyl alcohol) as blood vessel substitute (failure in experimental animals). *Surgery* 41: 729–737, May 1957.
45. HARRISON, J. H.: Synthetic materials as vascular prostheses: I. Comparative study in small vessels of nylon, Dacron, Orlon, Ivalon sponge and Teflon. *Am. J. Surg.* 95: 3–15, Jan. 1958.
46. HARRISON, J. H.: Synthetic materials as vascular prostheses. II. Comparative study of nylon, Dacron, Orlon, Ivalon sponge and Teflon in large blood vessels with tensile strength studies. *Am. J. Surg.* 95: 16–24, Jan. 1958.
47. JONES, T. W., STEVENSON, J. D., JESSEPH, J. E. and HARKINS, H. N.: Critical evaluation of polyvinyl sponge (Ivalon) as vascular and tissue substitute. *Am. Surgeon* 24: 401–414, May 1958.
48. ANDERSEN, M. N. and SENNING, A.: Study of reinforced Ivalon as prosthetic material for arterial replacement. *A.M.A. Arch Surg.* 79: 542–547, Oct. 1959.
49. KUNLIN, J.: Sur quelques inconvénients de l'Ivalon utilisé comme prothèse artérielle. *Mém. Acad. chir.* 82: 1047–1050, Dec. 12–19, 1956.
50. MARTIN, P. and GAYLIS, H.: Peripheral artery grafting; description of operation. *Brit. M. J.* 2: 371–376, Aug. 17, 1957.
51. MCCAUGHAN, J. J., JR.: Experimental use of Ivalon arterial grafts. *Surgery* 42: 717–721, Oct. 1957.
52. MCCAUGHAN, J. J., JR.: Unfavorable results with Ivalon arterial grafts in dogs. *Surgery* 45: 661–662, April 1959.
53. MORTON, J. H. and MAHONEY, E. B.: Long-term study of externally supported venous and arterial heterografts. *Surgery* 43: 381–387, March 1958.
54. MORTENSEN, J. D., EDWARDS, J. E., GRINDLAY, J. H. and KIRKLIN, J. W.: Reinforcement of fresh autogenous venografts to aorta; experimental study with polyvinyl formalinized (Ivalon) sponge. *A.M.A. Arch. Surg.* 70: 545–554, April 1955.
55. MORTENSEN, J. D., and GRINDLAY, J. H.: Molded, seamless tubes of polyvinyl formalinized sponge; their use as replacements for segments of aorta and major arteries. *A.M.A. Arch. Surg.* 72: 871–878, May 1956.
56. MURPHY, T. O., HAGLIN, J. J., LILLEHEI, C. W. and VARCO, R. L.: Role of surgery in treatment of arteriosclerosis of major vessels. *Minnesota Med.* 39: 703–709, Nov. 1956.
57. OHARA, I., TANNO, A. and SAKAI, T.: Experimental study on polyvinyl sponge grafts (Ivalon and polyvinyl-formal) transplanted into arterial defect with case of clinical application. *Angiology* 9: 129–135, June 1958.
58. OWEN, K.: Polyvinyl alcohol sponge as arterial substitute. *Proc. Roy. Soc. Med.* 49: 340–342, June 1956.
59. ROB, C. G.: Arterial substitutes. *Transpl. Bull.* 4: 51–53, April 1957.
60. ROB, C. G., EASTCOTT, H. H. G. and OWEN, K.: Reconstruction of arteries, *Brit. J. Surg.* 43: 449–466, March 1956.
61. SHUMWAY, N. E., GLEIDMAN, M. L. and LEWIS, F. J.: Experimental study of use of polyvinyl sponge for aortic grafts. *Surg. Gynec. & Obst.* 100: 703–706, June 1955.
62. SHUMWAY, N. E., LEWIS, F. J. and GLEIDMAN, M. L.: Plastic blood vessels made of polyvinyl sponge. *J. Lancet* 75: 348–350, Aug. 1955.
63. SMITH, F. R. and MCINTYRE, D.: Ivalon graft to bridge coronary artery occlusion. *J. Thoracic Surg.* 35: 513–516, April 1958.
64. STRUTHERS, A. M., GRINDLAY, J. H. and FIGI, F. A.: Experimental study of formation of autogenous bone within polyvinyl sponge. *Proc. Staff Meet. Mayo Clin.* 30: 462–466, Oct. 5, 1955.

65. Thurlow, A. A., Jr., Rapport, R. L. and Curtis, G. M.: Abdominal aneurysm wrapping with polyvinyl formal sponge; report of case with duodenal perforation. *A.M.A. Arch. Surg.* 65: 920–925, Dec. 1952.
66. Welch, J. S., Kirklin, J. W., Ellis, F. H. and Bruwer, A. J.: Resection and grafting for chronic occlusion of terminal aorta of iliac arteries, *J.A.M.A.* 164: 1045–1049, July 6, 1957.
67. Jones, T. W., Nyhus, L. M. and Harkins, H. N.: Formalinized polyvinyl alcohol (Ivalon) sponge in repair of liver and kidney wounds. *A.M.A. Arch. Surg.* 76: 583–588, April 1958.
68. Brown, J. B., Fryer, M. P. and Lu, M.: Polyvinyl and silicone compounds as subcutaneous prostheses; laboratory and clinical investigation. *A.M.A. Arch. Surg.* 68: 744–751, June 1954.
69. Freeman, B. S.: Complications following subcutaneous implantation of plastic sponge. *Plast. & Reconstruct. Surg.* 15: 149–153, Feb. 1955.
70. Hamit, H. F.: Implantation of plastics in breast; complications in case. *A.M.A. Arch. Surg.* 75: 224–229, Aug. 1957.
71. Johnson, H. A. and Grindlay, J. H.: Experimental alteration of nasal contour by use of polyvinyl sponge. *Plast. and Reconstruct. Surg.* 14: 293–297, Oct. 1954.
72. Moore, A. M. and Brown, J. B.: Investigation of polyvinyl compounds for use as subcutaneous prostheses. *Plast. & Reconstruct. Surg.* 10: 453–459, Dec. 1952.
73. Pangman, W. J., II, Wallace, R. M. and Hills, B.: Use of plastic prosthesis in breast plastic and other soft tissue surgery. *West. J. Surg.* 63: 503–512, Aug. 1955.
74. Amler, M. H., Johnson, P. L. and Bevelander, G.: Bone regeneration following grafts with polyvinyl plastic sponge. *Oral Surg.* 11: 654–661, April 1958.
75. Bryan, R. S., Janes, J. M. and Grindlay, J. H.: Effect of polyvinyl-formal (Ivalon) sponge on cortical bone healing. *Proc. Staff Meet. Mayo Clin.* 33: 453–457, Sept. 17, 1958.
76. Friedenberg, Z. B. and Lawrence, R.: Bone growth in polyvinyl sponge. *Surg. Gynec. & Obst.* 109: 291–294, Sept. 1959.
77. Popovici, A. F.: Polyvinyl plastic sponge in experimental orthopedic surgery; preliminary report. *Bull. Georgetown Univ. M. Center* 7: 177–181, May 1954.
78. Struthers, A. M.: Experimental study of polyvinyl sponge as substitute for bone. *Plast. & Reconstruct. Surg.* 15: 274–289, April 1955.
79. Dodge, H. W., Grindlay, J. H., Craig, W. M. and Ross, P. J.: Use of polyvinyl sponge in neurosurgery. *J. Neurosurg.* 11: 258–261, May 1954.
80. Donin, J. F., Henderson, J. W. and Grindlay, J. H.: Evisceration of eye with implantation of polyvinyl sponge; experimental study. *A.M.A. Arch. Ophth.* 54: 373–380, Sept. 1955.
81. Henderson, J. W.: Reconstruction of orbit with polyvinyl sponge. *A.M.A. Arch. Ophth.* 50: 714–717, Dec. 1953.
82. Kazdan, M. S., Henderson, J. W. and Parkhill, E. M.: Elevation of choroid by insertion of polyvinyl sponge; experimental study. *Am. J. Ophth.* 47: 437–453, Jan. 1959.
83. Pearlman, M. D.: Recommendations for utilization of polyvinyl plastic sponge as orbital implant. *Trans. Am. Acad. Ophth.* 57: 910–911, Nov.–Dec. 1953.

84. Benjamin, R. B. and others: Polyvinyl sponge in experimental surgery. *Ann. Surg.* 145: 509–516, April 1957.
85. Bing, J.: Tissue reaction to implanted plastics. *Acta path. et microbiol. scandinav.* Suppl. 105: 16–26, 1955.
86. Edwards, L. C., Pernokas, L. N. and Dunphy, J. E.: Use of plastic sponge to sample regenerating tissue in healing wounds. *Surg. Gynec. & Obst.* 105: 303–309, Sept. 1957.
87. Grindlay, J. H. and Waugh, J. M.: Plastic sponge which acts as framework for living tissue; experimental studies and preliminary report of use to reinforce abdominal aneurysms. *A.M.A. Arch. Surg.* 63: 288–297, Sept. 1951.
88. Martinez, N. S., Dahl, E. V. and Grindlay, J. H.: Early tissue responses to polyvinyl sponge aortic grafts; experimental study. *Surgery* 42: 1002–1013, Dec. 1957.
89. Petry, G. and Heberer, G.: Synthetic arterial prostheses in new vessel wall formation. *Langenbecks Arch. u. Deut. Zschr. Chir.* 286: 249, 1957. *Internat. Abst. Surg.* in *Surg. Gynec. & Obst.* 107: 185–186, Aug. 1958.
90. Schilling, J. A., Favata, B. V. and Radakovich, M.: Studies of fibroplasia in wound healing. *Surg. Gynec. & Obst.* 96: 143–149, Feb. 1953.
91. Adler, R. H. and Firme, C. N.: Use of pliable synthetic mesh in repair of hernias and tissue defects. *Surg. Gynec. & Obst.* 108: 199–206, Feb. 1959.
92. Harrison, J. H.: A Teflon weave for replacing tissue defects. *Surg. Gynec. & Obst.* 104: 584–590, May 1957.
93. Oppenheimer, B. S. and others: Further studies of polymers as carcinogenic agents in animals. *Cancer Res.* 15: 333–340, June 1955.
94. Oppenheimer, B. S. and others: Latent period in carcinogenesis by plastics in rats and its relation to presarcomatous stage. *Cancer* 11: 204–213, Jan.–Feb. 1958.
95. Oppenheimer, B. S. and others: Studies of mechanism of carcinogenesis by plastic films. *Acta Unio internat. contra cancrum* 15: 659–663, 1959.
96. Adler, R. H. and Firme, C. N.: Use of Nylon prostheses for diaphragmatic defects. *Surg. Gynec. & Obst.* 104: 669–674, June 1957.

(Part II, "Studies of Tensile Strength," will appear in the December issue.)

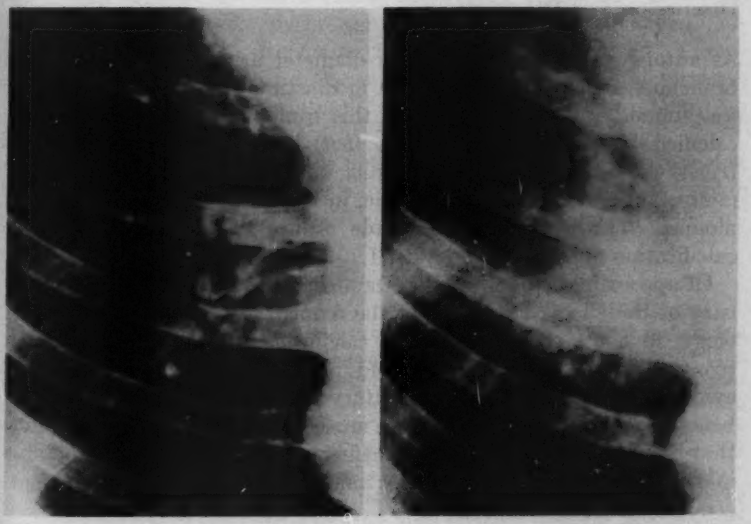
PROPER PERSPECTIVE

Can we honestly say that medicine, in spite of its great discoveries, has kept up with this modern world? Are our investigations into the cause of disease and its diagnosis and treatment really all that much better? We still take the blood pressure with an inflated cuff, which scientists tell me is full of inaccuracies.—Leslie A. Gibbons: Speaking Personally. *British Medical Journal*, November 28, 1959.

Case for Diagnosis

SAMUEL H. ROSEN, M.D.

A 54-year-old white man was admitted to the hospital emaciated, dyspneic, weak, and coughing frequently. He had suffered weight loss of 30 pounds and easy fatigability during the past 2 years. The left hilar shadow in the admission chest roentgenogram (*left*) was also present, although smaller, on a routine chest film taken about 2 years previously. Review of earlier films revealed a shadow in the same hilar region of a routine chest film (*right*) taken about 8 years previously. The patient died 1 month after admission.

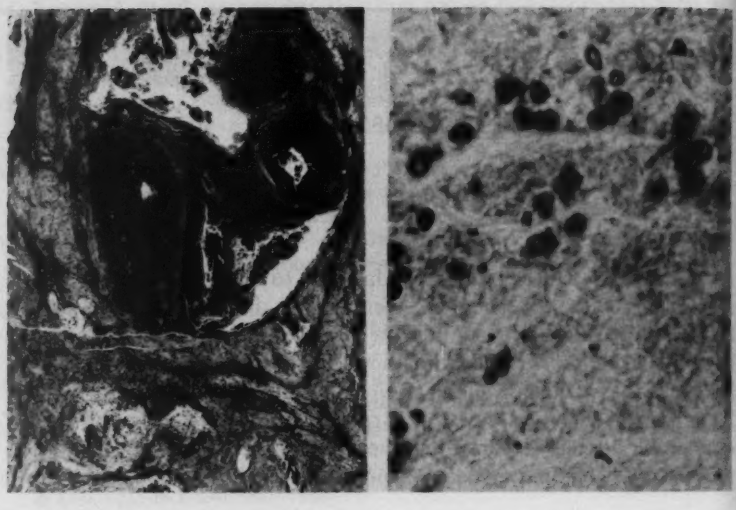


Diagnosis?

Please turn the page

From the Central Laboratory for Pathologic Anatomy and Research, Veterans Administration, Armed Forces Institute of Pathology, Washington, D.C. This month's Case for Diagnosis is AFIP Accession No. 632394, contributed by Veterans Administration Hospital, Fort Howard, Md.

562174 O—60——9



Discussion and Diagnosis

At autopsy a carcinoma 7 cm in diameter arising in the left main bronchus, with metastases to the mediastinum and the left kidney, was found. Incorporated within this tumor was a group of partly calcified histoplasma granulomas (*left*). The higher magnification (*right*) shows *Histoplasma capsulatum*, stained by the Gomori-Grocott methenamine–silver nitrate technic, in the center of one of the granulomas. The many sections made of the tumor failed to reveal calcification of the carcinoma itself.

Of approximately 750 cases of bronchogenic carcinoma in the Registry of Radiologic Pathology at the Armed Forces Institute of Pathology, in not a single instance is calcification of the tumor seen on roentgenogram. Although the old principle that roentgenographic evidence of calcification in a solitary mass in the lung indicates a benign lesion is still tenable, one must keep in mind the possibility that by incorporating a benign calcified lesion—such as the granuloma in this case—a malignant tumor may itself appear calcified roentgenographically.

Reference. O'Keefe, M. E., Jr., Good, C. A. and McDonald, J. R.: Calcification in solitary nodules of lung. *Am. J. Roentgenol.* 77: 1023–1033, June 1957.

Case Reports

Sprengel's Deformity

LIEUTENANT COLONEL JAMES D. CASKIE, MC, USA
COLONEL ROBERT D. ANDERSON, MC, USA

CONGENITAL ELEVATION OF THE SCAPULA, congenital high scapula, or undescended scapula is known as "Sprengel's deformity." [1] It is "characterized by the upward displacement of one or both scapulae with rotation upon the sagittal or frontal axis." [2] Originally described by Eulenburg [3] in 1863, Sprengel [4] in 1891, and by autopsy findings of Willet and Walsham [5] in 1880, this deformity has proved to be of great interest through the years. Schrock, [6] Smith, [7] Jeannopoulos, [8] and Blair and Wells [9] have rather thoroughly described the lesion, associated deformities, pathologic anatomy, roentgenographic findings, and treatment. Reporting 50 cases, Smith discussed the embryologic development and the surgical treatment of the deformity; Jeannopoulos concerned himself with the postoperative follow-up on 21 of 35 cases.

Although a long follow-up is not yet available on the case reported herein, the methods of work-up, photographic and roentgenographic documentation, and pathologic examination are thought to be instructive.

CASE REPORT

A 4-year-old white girl was admitted to the hospital 2 March 1959 for the surgical correction of a deformity of the left scapula. She had no complaints other than the deformity and limitation of motion of the left shoulder girdle. The past history was negative except for a benign tumor of the nose removed elsewhere at 1 month of age, leaving a noticeable scar of the right nostril. Family history was negative except for a 6-year-old brother who had been born with a cleft palate, subsequently repaired surgically.

Physical examination revealed a stellate scar on the right ala of the nose. The left shoulder was elevated and a palpable mass extended from the medial border of the left scapula to the sixth or seventh cervical vertebra (fig. 1). There was full range of motion of the neck, which appeared shortened. Abduction of the

From the Orthopedic Service, Fitzsimons General Hospital, Denver, Colo., Colonel Caskie is now assigned to 130th Station Hospital, APO 403, New York, N.Y.

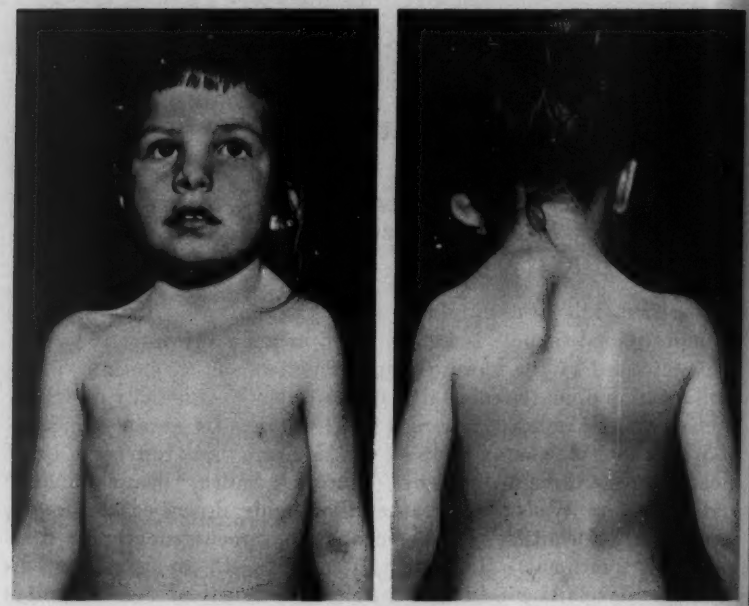


Figure 1. Sprengel's deformity. Prominent scapula and omovertebral bone are evident in posterior view.

left shoulder was limited to 70°. No scapular motion was possible. The patient was unable to reach the top or back of her head without lateral flexion rotation of the neck. No other abnormalities were noted.

Roentgenograms of the shoulders and upper thoracic and lower cervical spine in the anteroposterior, lateral, and oblique views revealed superior displacement of the left scapula with abnormal tenting of its vertebral borders, and a bony prominence, known as omovertebral bone, connecting the vertebral border of the scapula to the spinous processes of C5 and C6 (figs. 2–4). The omovertebral bone articulated mainly with C6; however, there was some fusion of the spinous processes of C5 and C6. The connection between spinous process and vertebral bone and between scapula and vertebral bone appeared ligamentous rather than bony. Fusion of the posterior arches of C5 and C7 as well as T3 was absent. No other abnormalities were seen. Multiple views of the cervical spine showed an elevated left scapula with hypoplasia of the first left rib and evidence of spina bifida of the lower cervical spine and of T3. There was a possibility of some congenital hemivertebrae as well, but this was difficult to interpret. The roentgenologist's diagnosis was Sprengel's deformity with omovertebral bone.

After numerous roentgenograms, multiple photographs, and other routine preoperative studies, the patient was operated on 5 March in the right lateral position. Through a 10-cm incision over the medial border of the scapula, an anomalous omovertebral bone was found to extend from the superomedial verte-

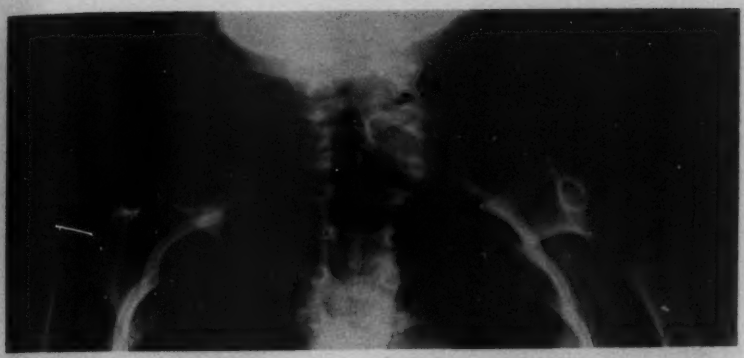


Figure 2. Anteroposterior view of shoulders, showing elevation of scapula.

bral border of the scapula to the spine of C6. This bone was excised by sharp and blunt dissection, extraperiosteally, with resultant marked improvement in scapular motion. The trapezius muscle was resutured to itself and the deep fascia was plicated over the inferior angle of the scapula to prevent winging. The scapula was not sutured inferiorly to a rib. The wound was otherwise

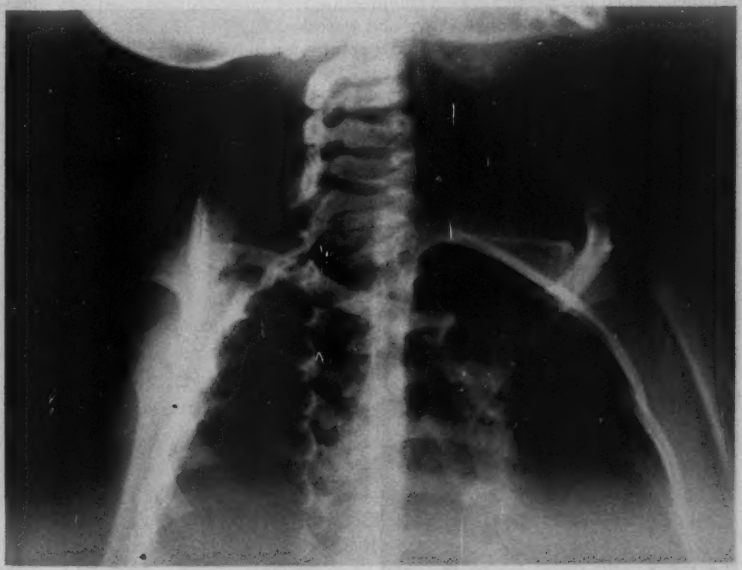


Figure 3. Oblique view of shoulders, showing omovertebral bone on right.

Figure 4. Lateral view of cervical spine, showing omovertebral bone and cervical anomalies.

routinely closed and dressed with a compression and figure-of-eight dressing. The patient made an uneventful recovery and was discharged on the seventh hospital day (the fourth postoperative day) to return for suture removal. Follow-up

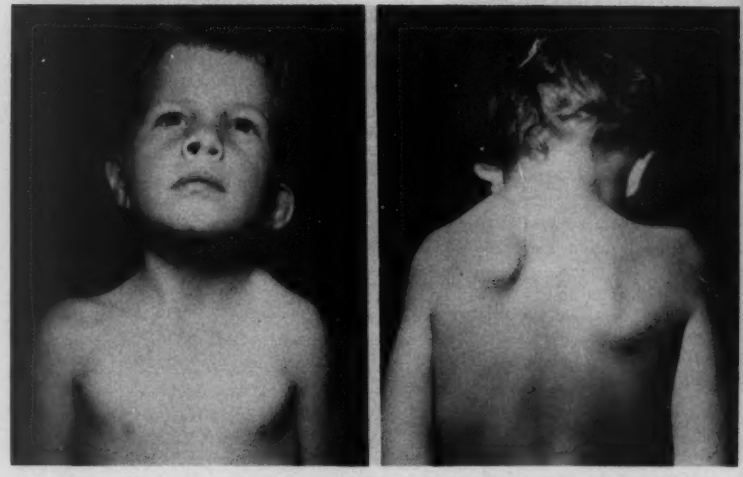


Figure 5. Appearance of patient after excision of omovertebral bone.

photographs (fig. 5), roentgenograms (fig. 6), and muscle tests made at 3 months indicated cosmetic and functional improvement, which will probably continue.

DISCUSSION

In the preoperative study of this patient, photographs confirmed the deformity. Roentgenograms indicated a somewhat peculiar-shaped omovertebral bone as described, and also revealed multiple anomalies of the cervical and upper thoracic spine, including spina bifida, fusion defects, and questionable hemivertebrae, considered by some consistent

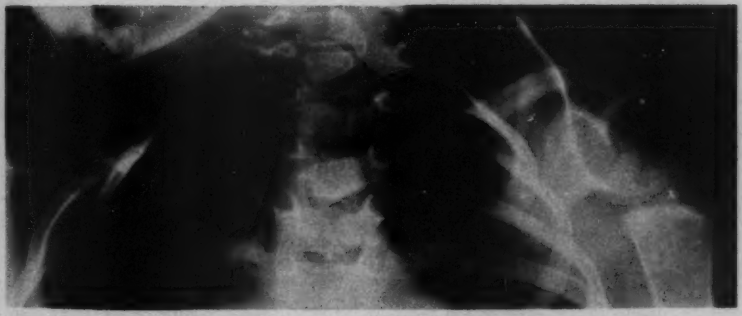


Figure 6. Postoperative roentgenogram, anteroposterior view.

with Klippel-Feil syndrome. These anomalies were seen in approximately 50 percent of the cases of Smith [7] and Jeannopoulos.[8] The omovertebral bone, which was excised, was seen in approximately 25 percent of cases. Interestingly enough, there are but 2 previous photographs of an excised omovertebral bone. Figure 7 is the third such reproduction, and the reproduced roentgenograms of the surgical specimen (fig. 8) are unique in the literature.

Pathologic examination of the specimen revealed normal bone surrounded by fibrous tissue on one side, with a cartilaginous cap at one end. Bone-marrow appeared normal and no other specific morphologic or pathologic abnormalities were noted. Review of the literature failed to reveal another pathologic examination of such a specimen.

The surgical procedure performed in this case was somewhat of a compromise on that recommended in the literature. Excision of the anomalous bone conforms to the treatment recommended by other authors. Partial excision of the spine and angle of the scapula

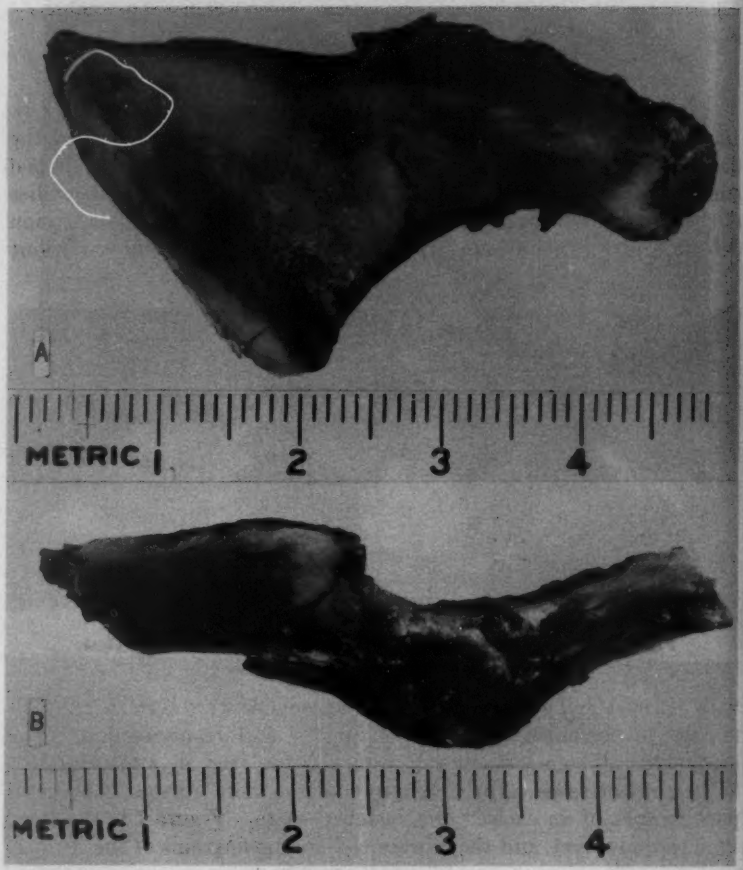


Figure 7. Surgical specimen. (A) Anteroposterior view. (B) Lateral view.

is a routine recommendation. In this case the scapula was not extensively stripped or sutured to a rib or fixed with a traction device to rotate the scapula downward. It was believed that the procedure as performed permitted cosmetic and functional improvement and that further improvement could be anticipated in a child of this age. However, if such improvement does not occur, resection and rotation can be performed at a later date, bearing in mind the possible complications, such as brachial plexus palsy or paralysis, keloid scar formation,

winging of the scapula, recurrence of the deformity because of regeneration of bone, or knoblike prominence of the sternoclavicular joint simulating a subluxation.[7, 8]

A new procedure, muscle origin "release" operation for congenital elevation of the scapula, recently reported by Woodward,[10] seems to have merit. Excellent functional and cosmetic results were obtained in the 6 cases reported. The technic consists of a long cervicothoracic midline incision, with detachment of the origins of the upper two thirds

Figure 8. Roentgenograms of surgical specimen.

of the trapezius and the major and minor rhomboids from the midline, where they form an aponeurosis. The superior angle of the scapula is nipped off without stripping, and the omovertebral bone or limiting band removed. The levator scapulae muscle is also released in the removal of the tip of the superior spine. The scapula is then depressed and the muscle sheet sutured at a lower level, as in the closure of any laminectomy. Such a procedure could be considered in this case.

SUMMARY

A case of Sprengel's deformity with omovertebral bone and cervical anomalies has been reported. The roentgenograms and pathologic report of the excised omovertebral bone are unique in the literature. The photograph of this excised bone is the third such reproduction in the literature.

ACKNOWLEDGMENT: The authors wish to commend and thank Mr. William R. Hommel and M/Sgt. Clarence Meier of the Medical Illustration Section of the Pathology Service, Fitzsimons General Hospital, Denver, Colorado, for their professional skill and kindnesses during the preparation of this paper.

REFERENCES

1. Ferguson, A. B.: *Orthopedic Surgery in Infancy and Childhood*, Williams & Wilkins, Baltimore, Md., 1957, pp. 188–191.
2. Horwitz, A. E.: Congenital elevation of the scapula—Sprengel's deformity. *Am. J. Orthopedic Surg.* 6: 260–311, Nov. 1908.
3. Eulenburg, cited by Horwitz.[2]
4. Sprengel, cited by Horwitz.[2]
5. Willet and Walsham, cited by Horwitz.[2]
6. Schrock, R. D.: Congenital elevation of scapula. *J. Bone & Joint Surg.* 8: 207–215, Jan. 1926.
7. Smith, A. DeF.: Congenital elevation of scapula. *Arch. Surg.* 42: 529–536, March 1941.
8. Jeannopoulos, C. L.: Congenital elevation of scapula. *J. Bone & Joint Surg.* 34–A: 883–892, Oct. 1952.
9. Blair, J. D. and Wells, P. O.: Bilateral undescended scapula associated with omovertebral bone; report of case. *J. Bone & Joint Surg.* 39–A: 201–206, Jan. 1957.
10. Woodward, J.: Muscle origin "release" operation for congenital elevation of scapula, presented at 27th Annual Meeting, American Academy of Orthopaedic Surgeons, Chicago, Ill., Jan. 1960, paper 32, p. 57.

Gonococcic Endocarditis

LIEUTENANT BENJAMIN J. GILSON, MC, USN
LIEUTENANT MONROE E. TROUT, MC, USN
LIEUTENANT HOWARD ALLEMAN, MC, USN

THE MORE OPTIMISTIC OUTLOOK for cure of gonococcic endocarditis since the advent of antibiotic therapy has increased interest in establishing the diagnosis of this relatively rare condition. Before this, the prognosis was uniformly poor. The following case report of endocarditis bacteriologically proved to be caused by *Neisseria gonorrhoeae* is presented in this perspective.

CASE REPORT

A 19-year-old single, enlisted white man was admitted to this hospital on 6 July 1959, with complaints of mild frontal headache of 11 days' duration, accompanied by sore throat, moderate stiffness and pain in both knees, flank pain, and pain in the dorsum of the right foot and in the lateral aspect of the left forearm. Positive findings at onset included low-grade fever, erythrocyte sedimentation rate of 30 mm per hour, and tenderness to palpation in the painful areas described. Treatment before admission consisted only of salicylates.

Past history included multiple attacks of tonsillitis and cutaneous infections. An episode of tonsillitis had occurred 3 weeks before admission to the hospital. Rheumatic fever in all its manifestations was denied. The patient admitted to sexual exposure several weeks before admission. He denied previous venereal disease. The patient's father had died of rheumatic heart disease, and a first cousin had a residual murmur from rheumatic heart disease.

Examination on admission revealed a well-developed and well-nourished, dark-complexioned white youth, who did not appear acutely ill. Blood pressure was 130/68 mm Hg, pulse rate 104 per minute, respiratory rate 20 per minute, and temperature 101.2°F. The throat was moderately injected and showed moderate tonsillar hypertrophy. Coarse bronchial basilar breath sounds were heard bilaterally. Examination of the heart revealed sinus tachycardia without enlargement or thrill. The aortic second sound was louder than the pulmonic. A soft systolic murmur, grade 2 on a scale of 6, was heard over the apex and also over the aortic area, radiating to the base of the neck. Abdominal examination was unremarkable except for mild tenderness to palpation deep in the left lower quadrant. There was marked tenderness to palpation and passive motion at the lateral aspect of the left forearm and right wrist. Examination of the genitalia and rectum was normal at the time of admission.

Laboratory studies on admission revealed an erythrocyte sedimentation rate of 45 mm per hour, hemoglobin of 12.5 grams per 100 ml, and white blood cell

From the Medical Department of U.S. Naval Hospital, Navy No. 3923, FPO San Francisco, Calif. Presented December 1959 at the Ninth Pacific Air Forces Medical Conference, Baguio, Philippine Islands.

count of 10,300 per cu mm, with a normal differential count. The Kahn test was negative. The urinalysis was unremarkable and revealed a specific gravity of 1.012. More detailed laboratory work considered normal or negative included the following: blood smears for malarial parasites, stool examination for ova and parasites, LE cell preparations of the peripheral blood, sputum smears stained for acid-fast bacilli, clinical and laboratory examination of lumbar spinal fluid, electrocardiograms, and roentgenograms of the chest. Throat culture showed alpha streptococcus to be the predominant organism. The antistreptolysin-O titer was 320 units. During the first 12 days a total of 12 blood samples were taken for culture and implanted on both aerobic and anaerobic media. The blood samples were taken in groups, attempts being made to obtain them during a rising phase of the temperature curve. Three of these yielded only nonpathogens with the appearance of air-borne contaminants.

A culture of blood inoculated on the twelfth day of hospitalization on trypticase soy broth and subcultured on chocolate agar under carbon dioxide tension was morphologically and culturally identified as *N. gonorrhoeae* on the thirty-first hospital day. The organism did not grow at room temperature and yielded the following biochemical reactions: oxidase test positive; glucose fermented, yielding acid; sucrose not fermented; and maltose not fermented.

From the time of his admission, the patient had a febrile course, his temperature spiking sharply once and sometimes twice daily as high as 102°F. Intermittent pains in both knees and legs and in the left forearm persisted. Treatment during the first 12 days of hospitalization consisted only of rest in bed and an occasional dose of aspirin without apparent benefit.

During the first week of his hospital course a watery urethral discharge was noted. This showed only a few pus cells on Gram's stain. Culture of the discharge produced no organism. Following the institution of antibiotic therapy, this discharge did not recur, and further studies were not possible.

On the twelfth hospital day, during an episode of shaking chills and temperature of 102°F., the last 4 of 12 blood cultures were taken. Empiric chemotherapy was then started, considered justified by the clinical evidence of an ominously progressive, septic clinical course. With the organism unknown, erythromycin and chloramphenicol were selected, each 2 grams daily in divided doses by mouth.

During an afebrile period on the fifteenth hospital day, definite changes in the heart sounds were heard. The systolic murmur had become loud, blowing, and harsh, with maximal intensity at the apex and along the left sternal border. The pulmonic second sound became louder than the aortic. There was no accompanying thrill, and the electrocardiographic tracings remained normal. The erythrocyte sedimentation rate was then 46 mm per hour.

A rapid response to chemotherapy was noted. On re-evaluation of the patient, it was thought that penicillin was the drug of choice, because of its bactericidal nature and the possibility of endocarditis. Since the patient was unable to tolerate a trial of 2 million units of aqueous crystalline penicillin intramuscularly every 3 hours, he was treated, beginning on the twenty-fourth hospital day, with a continuous intravenous drip of 18 million units for each 24-hour period, easily divided among three 1-liter bottles of 5 percent dextrose and water.

On the thirty-first day, as previously noted, *N. gonorrhoeae* was identified in the blood culture. On the thirty-third hospital day the temperature curve became established below the level of 99°F, and the systolic murmur reached its maximal intensity, being heard over the entire precordium, with an associated apical thrill. The thrill gradually disappeared, lasting for only 3 days.

The intravenous administration of penicillin was discontinued after 6 weeks, with a total dose of 732 million units. The total dose of erythromycin and chloramphenicol was 34 grams of each, preceding and overlapping the penicillin regimen by several days.

During the period of penicillin treatment, the murmur became stabilized as a moderately loud (grade 3 on a scale of 6), coarse systolic murmur, maximal at the third interspace and at the apex, with radiation to the aortic area. No diastolic component to the murmur was heard during the patient's hospital stay. At no time were there signs of peripheral emboli, palpable splenomegaly, or congestive failure.

Following discontinuance of pencillin therapy, the electrocardiograms, erythrocyte sedimentation rates, and temperature curve remained within normal limits. Four spaced blood cultures were sterile. The patient was followed for 2 additional weeks and then transferred on 21 September to a hospital within the continental limits of the United States. A report from the U.S. Naval Hospital, Great Lakes, Illinois, indicated no essential change in clinical or laboratory status during the following 2 months.

COMMENT

Reports of gonococcic endocarditis are uncommon today. In an impressive review of the literature for the years 1936 through 1948, Jones [1] found 42 detailed case histories plus 39 cases mentioned, with a total of 7 apparent recoveries during that period. After Myers' report [2] of a patient successfully treated with penicillin, Dorset, Spicknall and Terry [3] presented a patient treated with penicillin and sulfadiazine; and Davis and Romansky [4] reported successful treatment with erythromycin. We have found no other cases in the English language literature during this period of time.

In this case, the primary differential problem lay between acute rheumatic fever, subacute bacterial endocarditis, and an endocarditis of unknown etiology. Before institution of chemotherapy, there were few convincing criteria pointing exclusively to any of these diagnoses. The strong family history, the past history of recurrent tonsillitis, the polyarticular symptoms, and the elevated antistreptolysin-O titer favored the diagnosis of rheumatic fever.

On the other hand, the febrile pattern was an irregular one, with wide variations, and the patient exhibited persistent symptoms, generally in the same joint areas, rather than the migratory and transitory arthralgias usually characteristic of rheumatic fever. Salicylates had no effect. Negative findings, including the absence of subcutaneous nodules, splenomegaly, embolic phenomena, and petechial spots, gave little differential diagnostic help. After chemotherapy was begun, the changing heart sounds were considered to be highly suggestive of endocarditis. The urethral discharge, slight and brief as it was, was not considered suggestive except in retrospect; and

even then it could not be considered proof of the site of entry. The positive identification of the gonococcus in the blood culture gave the unequivocal diagnosis. The most important factor in the diagnosis and treatment of this patient was, without a doubt, a high index of suspicion.

The initial choice of chloramphenicol and erythromycin indicated clinical indecision at the start of the treatment. The septic clinical course and suspicion of endocarditis were sufficient to warrant empiric therapy, since it is generally agreed that early diagnosis and institution of treatment are most important for ultimate success.[5, 6] Also, although this is not the usual treatment for rheumatic fever, it was thought that no harm would follow the use of these drugs.

Penicillin was chosen as the primary therapeutic agent because it is bactericidal, whereas the others are considered bacteriostatic.[5] After identification of the organism, the possibility of a penicillin-resistant gonococcus was considered, particularly because of the widespread use of penicillin in this area for venereal disease, and because recent clinical failures in the treatment of acute gonorrhea have been reported in American troops in Korea.[7, 8] The clinical course, however, reflected the success of the therapy, the primary criteria for success being the temperature response, clinical signs on auscultation of the heart, and subsidence of laboratory evidence of infection.

SUMMARY

Reports of gonococcic endocarditis are rare. A high index of suspicion is imperative for diagnosis and early treatment, with rheumatic fever prominent in the differential diagnosis. In the case of gonococcic endocarditis presented here, the diagnosis was made on the basis of a single positive blood culture, 11 previous cultures having been negative; the cultural characteristics of the organism were convincing. Because of the septic course, empiric treatment with erythromycin and chloramphenicol was begun before the organism was identified, and later, when endocarditis was suspected, penicillin was instituted by continuous intravenous drip. The patient showed good clinical and bacteriologic response to chemotherapy.

REFERENCES

1. Jones, M.: Subacute bacterial endocarditis of nonstreptococcic etiology; review of literature of 13-year period 1936–1948 inclusive. *Am. Heart J.* 40: 106–116, July 1950.
2. Myers, W. K.: Penicillin therapy of gonococcic endocarditis of pulmonary valve. *J.A.M.A.* 133: 1205–1207, April 19, 1947.

3. DORSET, V. J., SPICKNALL, C. G. and TERRY, L. L.: Penicillin therapy of gonococcic endocarditis; case report. *Am. Heart J.* 38: 610–613, Oct. 1949.
4. DAVIS, D. S. and ROMANSKY, M. J.: Successful treatment of gonococcic endocarditis with erythromycin; review of literature. *Am. J. Med.* 21: 473–480, Sept. 1956.
5. FINLAND, M.: Treatment of bacterial endocarditis; dosage of penicillin, use of other antibiotics and treatment of patients with negative blood cultures. *Circulation* 9: 292–299, Feb. 1954.
6. FEDER, I. A.: Treatment of subacute bacterial endocarditis with negative blood cultures. *Am. J. Med.* 18: 602–607, April 1955.
7. EPSTEIN, E. E.: Failure of penicillin in treatment of acute gonorrhea in American troops in Korea. *J.A.M.A.* 169: 1055–1059, March 7, 1959.
8. ANON.: Penicillin-resistant gonococci. (Editorial) *New England J. Med.* 259: 302–303, Aug. 7, 1958.

Malignant Islet Cell Adenoma of Pancreas With Hypoglycemia

COLONEL CHING-CHANG LIU, MC
CAPTAIN CHU-CHIAO CHANG, MC

TUMORS OF THE ISLETS OF LANGERHANS may produce characteristic symptoms of hypoglycemia. Although the exact incidence of islet cell tumors of the pancreas is not known, they make up only a small fraction of all neoplasms of the pancreas [1] and are seldom seen in China. In 1927, Wilder [2] described a laparotomy performed at the Mayo Clinic on a hypoglycemic physician, in whom a malignant tumor of the pancreas was found. In 1929 the first islet cell adenoma was removed at the Toronto General Hospital, with complete relief of symptoms.[3,4] Since that time many cases of islet cell tumors have been documented.[3-7]

CASE REPORT

The patient, a Chinese officer, 38 years of age, was in good health until 2 months before admission to this hospital, when he noted the onset of attacks of faintness with loss of consciousness. The first attack occurred one morning before breakfast in July 1959 and was temporarily relieved by a solution injected by a civilian general practitioner. Since that time, the patient suffered attacks of faintness but without loss of consciousness. In each instance, the symptoms were relieved

From Second Army General Hospital of China, P.O. Box 7441, Kaohsiung, Taiwan, Republic of China.

spontaneously after some hours of bed rest. The last attack occurred in the hospital and was promptly relieved by the intravenous administration of 50 percent dextrose solution. The blood sugar level during that attack was 35 mg per 100 ml. The first fasting blood sugar level on the second day of admission was 45 mg per 100 ml, and subsequent determinations were all below 50 mg per 100 ml. Multiple furuncles occurred during the last 2 weeks. There was no weight loss. Appetite was described as normal.

On physical examination the patient was found to be a poorly nourished man who appeared to be chronically ill. There was no evidence of jaundice. No palpable lymph nodes were found in the cervical or axillary regions. Neck and chest were essentially negative. A soft, fixed, nontender mass, measuring more than 20 cm in diameter, was palpable in the left upper part of the abdomen and extended to the umbilicus. The liver and spleen were not palpable. Many furuncles were found on the skin of the upper and lower extremities. Roentgenographic study of the gastrointestinal tract revealed marked displacement of the stomach toward the right side.

Because of the size of the mass and persistent hypoglycemia, islet cell tumor of the pancreas was postulated. An exploratory laparotomy was performed on 3 September. Exposure of this mass revealed that it was a well-encapsulated, solitary tumor connecting with the tail of the pancreas. It was removed entirely by sharp dissection. The head of the pancreas and the liver were palpated but no abnormalities were found. The patient recovered from the surgical procedure and the postoperative course was uneventful. The subsequent blood sugar level determinations were all in the 85–100 mg per 100 ml range. When the patient was discharged from the hospital on 3 October, the multiple furuncles had subsided entirely and his general condition was much improved. To date, he is living, well, and has experienced no further hypoglycemic symptoms. He is receiving close follow-up.

Examination of the surgical specimen (fig. 1A) revealed that it was a well-encapsulated tumor, measuring 21 cm in diameter and weighing 1,560 grams. The outer surface was pinkish in color, because of an abundant capillary circulation. Bisection of the mass (fig. 1B) revealed the tissue to be homogeneous, grayish white in color, and friable like brain tissue. No cavity or calcification was present. Microscopically (fig. 2), the tumor was composed of sheets and cords of polyhedral cells with large relatively hyperchromatic nuclei and a scanty amount of cytoplasm. The cells were uniform in appearance and separated by a delicate

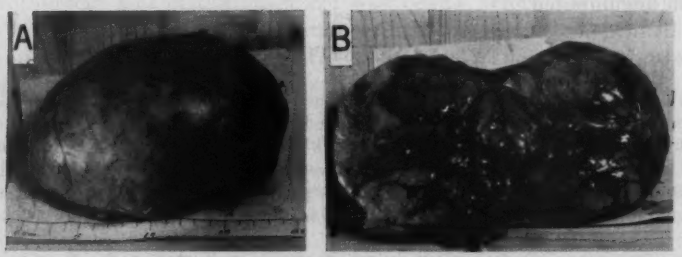


Figure 1. Malignant islet cell adenoma of pancreas, pathologic specimen No. 1614. (A) Gross appearance. (B) Bisection.

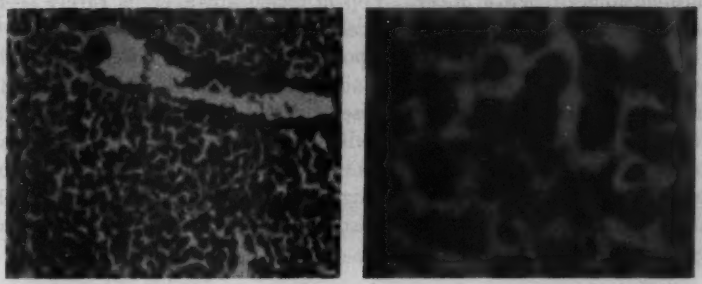


Figure 2. Malignant islet cell adenoma. Sheets and cords of polyhedral cells with large hyperchromatic nuclei.

stroma of capillaries and a scanty amount of fibrous tissue. No venous invasion was present but numerous mitotic figures were found. The pathologic diagnosis was malignant islet cell adenoma.

DISCUSSION

The islets of Langerhans, although scattered throughout the pancreas, are particularly numerous in the tail. The islets have no capsule and are separated from the acinar and ductal cells only by the basement membrane of the acinar cells and by the interlobular fibrous tissue. With special staining, granulations are demonstrated and 4 types of islet cells are classified. They are: (1) alpha cells, (2) beta cells, (3) delta cells, and in some species (4) nongranular or indifferent cells. It is now accepted that the beta cells elaborate insulin, and considerable evidence suggests but does not prove that the alpha cells are the site of synthesis of the hyperglycemic-glycogenolytic factor, glucagon.[8] The function of the delta cells and indifferent cells is unknown. Neoplasms of islet cells with hypoglycemia, therefore, are functioning adenomas or carcinomas of the beta cells. The nonfunctioning neoplasms of the islets consist either of beta cells without signs of granulation or of other cells of the islets.

The relative incidence of functioning as opposed to nonfunctioning neoplasms of the islets has not been established because the islet cell tumors encountered at operation are predominantly a selection of functioning neoplasms. In a series of 398 cases [5] collected from the literature, there were 15 cases without evidence of overproduction of insulin. Donaldson and others [9] reported 2 cases of islet cell carcinoma of the pancreas not productive of insulin, with severe gastric hypersecretion and hyperacidity and recurrent gastrojejunal ulceration. These patients required numerous surgical procedures for

562174 O—60——10

complications of peptic ulcer. Peptic ulcer, however, is rarely seen with hyperinsulinism due to beta cell carcinoma or adenoma.

Islet cell tumors with severe hypoglycemia may be classified as follows:[3] (1) islet cell adenoma, (2) adenomatosis of the islets, and (3) carcinoma of islets. Between the second and third groups there is an additional group, which may be called indeterminate or possibly malignant adenoma. Some of these tumors appear to be malignant histologically, but their behavior is benign. In 200 cases[10] of hyperinsulinism resulting from anatomic disorders of islets the following lesions were found:

Diffuse adenomatosis	4%
Adenoma, benign	75%
Adenoma, "semibenign" (clinical course benign, histologically malignant)	11%
Carcinoma	10%

The patient reported herein had a tremendous tumor in the tail of the pancreas with severe clinical symptoms of hypoglycemia. Blood sugar level, either fasting or during attacks, was usually below 50 mg per 100 ml. Roentgenologic study showed evidence of pancreatic neoplasm with displacement of stomach toward the right side. Although the electroencephalogram was not made, brain damage was evident clinically. Because of its rapid growth, large size, and numerous mitoses, the histologic diagnosis was malignant adenoma of islets. Postoperatively, however, this patient is perfectly well and has had no further attacks of hypoglycemia. The tumor was found to be a solitary well-encapsulated one without any evidence of regional metastases. Therefore, we believe that this islet cell tumor is a malignant adenoma.

Islet cell tumors are usually located in the tail of the pancreas (74%),[10] and the size of islet cell tumors, including carcinomas, is usually small, the average diameter being 1 to 2 cm. An exceptional case found in the literature was a benign islet cell adenoma 15 cm in diameter, weighing 673 grams.[10] The tremendous solitary tumor in our patient was 21 cm in diameter and weighed 1,560 grams, and as far as we know is the largest functioning islet cell tumor reported. There is no relationship between the size of the tumor and the severity of the hyperinsulinism, but in an islet cell tumor over 3 cm in diameter malignancy should be suspected.[4]

SUMMARY

The functioning islet cell tumor is a rare neoplasm of the pancreas, especially in China. A case of functioning islet cell tumor weighing

1,560 grams that was successfully excised is presented. The histologic structure, clinical course, and factors concerning the functions and malignancy of islet cell tumors are discussed.

REFERENCES

1. Ackerman, L. V.: *Surgical Pathology*, C. V. Mosby Co., St. Louis, Mo., 1953, p. 409.
2. Wilder, R. M. and others: Carcinoma of islands of pancreas, hyperinsulinism and hypoglycemia. *J.A.M.A.* 89: 348–355, July 30, 1927, cited by Boyd.[3]
3. Boyd, W: *Pathology for the Surgeon*, ed. 7, W. B. Saunders Co., Philadelphia, Pa., 1955, pp. 273–274.
4. Porter, M. R. and Frantz, V. K.: Tumors associated with hypoglycemia—pancreatic and extra-pancreatic. *Am. J. Med.* 21: 944–961, Dec. 1956.
5. Howard, J. M., Moss, N. H. and Rhoads, J. E.: Collective review; hyperinsulinism and islet cell tumors of the pancreas with 398 recorded tumors. *Internat. Abstr. Surg.* 90: 417–455, 1950; in *Surg., Gynec. & Obst.* May 1950.
6. Whipple, A. O. and Frantz, V. K.: Adenoma of islet cells with hyperinsulinism; review. *Ann. Surg.* 101: 1299–1335, June 1935.
7. Frantz, V. K.: Tumor of islet cells with hyperinsulinism, benign, malignant, and questionable. *Ann. Surg.* 112: 161–176, Aug. 1940.
8. Lazarow, A., in Williams, R. H. (editor): *Diabetes*, Paul B. Hoeber, Inc., New York, N.Y., 1960, pp. 41–42.
9. Donaldson, R. M., Jr., von Eigen, P. R. and Dwight, R. W., cited by Johnson, T. A. and Kalser, M. H.: Pancreas; contributions of clinical interest. *Castroenterology* 36: 295–332, March 1959.
10. Twiss, J. R. and Oppenheim, E.: *Practical Management of Disorders of the Liver, Pancreas, and Biliary Tract*, Lea & Febiger, Philadelphia, Pa., 1955 p. 543.

Oxyphil Cell Tumor of Submaxillary Gland

CAPTAIN JOHN G. BATSAKIS, MC, USA
CAPTAIN DOUGLAS G. MARTZ, MC, USA

OXYPHIL CELL TUMORS of the salivary glands are among the least common of the benign tumors that occur in these sites. Whereas mixed tumors constitute approximately 80 percent of the benign tumors of the parotid gland, oncocytic adenomas (oncocytomas) make up less than 1 percent of parotid tumors.[1] The origin of such a tumor in a salivary gland other than the parotid is of even rarer occurrence. It is the purpose of this report to record such a lesion and to discuss its histogenesis briefly.

From the Laboratory Service, Walter Reed General Hospital, Washington, D.C.

CASE REPORT

A 79-year-old white man was admitted to the otolaryngology service of this hospital because of a persistent left submandibular mass. The patient had noted a persistent asymptomatic enlargement in the left submaxillary gland region for the preceding 20 years. Eight months before this admission to the hospital and following an upper respiratory infection, the mass gradually increased in size, with no associated pain or tenderness.

On examination, a 2- by 3-cm, firm, freely movable, nontender left submandibular mass was palpated. No drainage from the gland could be obtained by pressure, and roentgenograms revealed no calculi obstructing the duct.

Two days following admission, under general anesthesia, a hard fibrotic and lobulated left submaxillary gland was surgically removed. Gross examination of the specimen, which measured 5.5 by 3.0 by 2.5 cm and weighed 15 grams, revealed the normal lobulated architecture of the anterior half of the gland replaced by a round, circumscribed pink-tan tumor with scattered microcystic areas. No calculi were found.

Microscopic examination of sections stained with hematoxylin and eosin revealed a well-circumscribed tumor, uniformly composed of large oxyphilic cells in solid masses and in an acinar arrangement (fig. 1). These cells contained

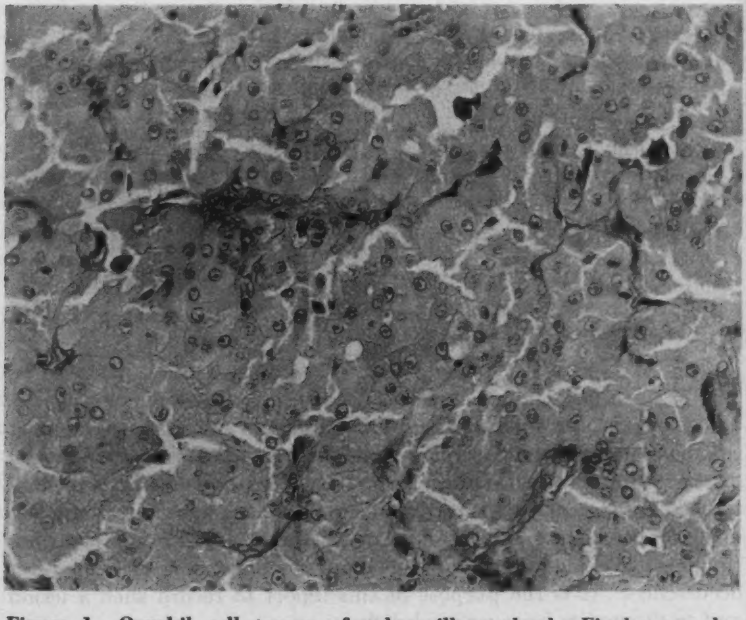


Figure 1. Oxyphil cell tumor of submaxillary gland. Finely granular oxyphilic cytoplasm and prominent cell borders. Fine vascular septums separate cords and acini. (Hematoxylin and eosin, x 240)

abundant finely granular cytoplasm and centrally placed, benign-appearing nuclei. Their derivation from both ductal and acinar elements could be identified. Thin vascular septums traversed the cords of the neoplasm.

DISCUSSION

Of a total of 877 major salivary gland tumors observed at the Memorial Center for Cancer and Allied Diseases, New York, N.Y., between 1930 and 1949, only 1 oxyphil adenoma was recorded, and this arose in the parotid gland.[2] Although the occurrence of similar oncocytic tumors in salivary glands other than the parotid is not entirely unexpected, Foote and Frazell [2] cited only 1 such instance in their survey.

Hamperl [3] believes that this cell type is associated with advancing age and consequent glandular atrophy. He has found such cells in all major and minor salivary glands as well as in other organs of the body. Tumors composed of oncocytic cells are apparently found only in patients above the age of 50 years. This age incidence is consistent with the observation that oncocytes are extremely rare before 50 and have never been found in patients under 20 years of age.[4] In a study of 100 parotid glands from the necropsy series at the University of Michigan Hospital, Meza-Chavez [5] confirmed the presence of oxyphil cells with advancing age in 9 of 51 patients; he also demonstrated that both ductal and acinar cells are involved. Although there is no definite answer concerning the significance of oxyphilic granular cells, the consensus appears to concur with Hamperl [3] that they represent a degenerative or atrophic change in the involved cells.

The similarity of oncocytic cells to the epithelial elements of papillary cystadenoma lymphomatosum has prompted the suggestion that the 2 lesions are related. Against this theory are the observation that the latter tumor consists of 2 distinct histologic components, epithelial and lymphoid, and the much higher reported incidence of Warthin's tumor.

Finally, whether the tumors formed by these cells should be considered true neoplasms or a form of hyperplasia is not entirely clear. Despite the acknowledged occurrence of oncocytes singly or in groups as an accompaniment of advancing age, it seems reasonable to conclude that the variety with clinical manifestations and the morphologic appearance of a tumor, as seen in our patient, represents neoplasia rather than hyperplasia.

Characteristically, these tumors follow a benign course and show no recurrence unless incompletely excised.[6]

SUMMARY

A case of oxyphil cell adenoma of the submaxillary gland with a brief review of histogenesis and the pertinent literature is presented. These rare neoplasms, benign in nature and apparently occurring only in elderly patients, are derived from both ductal and acinar elements of the glands. Their characteristic cytomorphology is related to regressive changes in the involved cells.

REFERENCES

1. Beahrs, O. H., Devine, K. D., Woolner, L. B. and Bulbulian, A. H.: Tumors of parotid gland; their surgical management. *A.M.A. Arch. Surg.* 79: 900–914, Dec. 1959.
2. Foote, F. W., Jr., and Frazell, E. L.: Tumors of the Major Salivary Glands, in *Atlas of Tumor Pathology*, Armed Forces Institute of Pathology, Washington, D.C., under the auspices of the Subcommittee on Oncology of the Committee on Pathology, National Research Council, Washington, D.C., 1954, Sec. 4, fasc. 11, p. 139.
3. Hamperl, H.: Über das Vorkommen von Onkocyten in verschiedenen Organen und ihren Geschwülsten (Mundspeicheldrüsen, Bauchspeicheldrüse, Epithelkörperchen, Hypophyse, Schilddrüse, Eileiter). *Virchows Arch. f. path. Anat.* 298: 327–375, 1936.
4. Chaudhry, A. P. and Gorlin, R. J.: Papillary cystadenoma lymphomatosum (adenolymphoma); review of literature. *Am. J. Surg.* 95: 923–931, June 1958.
5. Meza-Chavez, L.: Oxyphilic granular cell adenoma of parotid gland (oncocytoma); report of 5 cases and study of oxyphilic granular cells (oncocytes) in normal parotid glands. *Am. J. Path.* 25: 523–547, May 1949.
6. Ackerman, L. V.: Oncocytoma of parotid gland. *Arch. Path.* 36: 508–511, Nov. 1943.

Urethral Foreign Body

CAPTAIN WILLIAM E. FRASER, MC, USN
LIEUTENANT ALLAN ERDE, MC, USN

FOREIGN BODIES in the bladder and urethra are common and will continue to be found in the lower genitourinary tract as long as people are erotic, drunk, curious, or desperate. The variety of such objects reported in the past range from squirrel tail bones to pins.[1]

From U.S. Naval Hospital, U.S. Naval Air Station, Jacksonville, Fla.

Recently, a 4¾-inch steel nutpick (fig. 1) was successfully removed with a hemostat from the urethra of a male patient.

CASE REPORT

The patient, a 50-year-old retired Air Force master sergeant, was admitted to the emergency room of this hospital because a nutpick had lodged in his urethra. He stated that he had used the nutpick to remove 2 "half-pea-sized" calculi from the distal urethra, and was pursuing the third stone when he became "nervous." At this juncture the do-it-yourself extractor was sucked out of his grasp, deeper into the urethra. This intensified the patient's nervousness, and he grasped the end of the penis as the pointed end of the nutpick disappeared from his view. In so doing, the distal sharply pointed end of the pick became firmly embedded in the glans penis, the point coming to lie just beneath the surface of the glans lateral to the urethral meatus, where it was easily palpable.

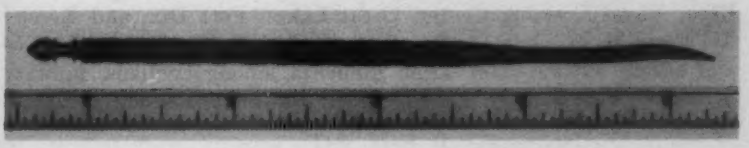


Figure 1. Photograph of nutpick removed from urethra.

Removal of the nutpick was effected without difficulty with a small hemostat by grasping the shaft of the pick, pushing it further into the urethra to disengage the tip from the glans, and carefully extracting the object. A postextraction roentgenogram of the genitourinary tract confirmed the presence of a 4-mm by 3-mm calculus in the bladder, thereby removing this patient from the erotic group.

SUMMARY

A case is presented in which a nutpick, used by a male patient for extracting calculi from his urethra, became impacted in the glans penis and had to be removed with a hemostat.

REFERENCE

1. Campbell, M. (editor): *Urology.* W. B. Saunders Co., Philadelphia, Pa., 1954 vol. 1, pp. 848–850.

Activities of the Commission on Influenza

FRED M. DAVENPORT, M.D.

DURING 1959–60, studies on the etiology, pathogenesis, epidemiology, and prevention of acute respiratory diseases were carried out, in collaboration with the military services, at Fort Ord; Lowry Air Force Base; Naval Training Center, Great Lakes; Fort Dix; and Keesler Air Force Base. It was clear that despite the occurrence of sharp and severe outbreaks of Asian influenza among civilians, military personnel were largely spared, owing to the protection conferred by vaccination.

POPULATIONS UNDERGOING BASIC TRAINING

At Fort Dix, where adenovirus vaccines were used first on a routine basis in recruits, the rate of adenovirus infections remained low until the supply of vaccine was exhausted. Fortunately, the outlook for adequate supplies of adenovirus vaccine is promising and it is anticipated that by vaccination of recruits against adenovirus infections and by service-wide vaccination against influenza, the respiratory disease rates in 1960–61 will be greatly reduced on posts where recruit training is carried out. Such suppression of influenza and of adenovirus infections should greatly enhance the likelihood of success in attempting to identify the nature of the "other" viral respiratory infections that are so troublesome in these populations.

Those responsible for immunization of recruit populations will be interested to know that a high degree of efficacy was demonstrated in field trials of vaccines that contained influenza and adenoviruses combined in a single preparation. The practical advantages of such a combined vaccine are obvious. Firm protection against Asian influenza and against adenovirus infection was established in controlled

---

From the Commission on Influenza, Armed Forces Epidemiological Board, Washington, D.C. Dr. Davenport, director of this Commission, is at the School of Public Health, University of Michigan, Ann Arbor.

studies carried out at Lowry Air Force Base, by Dr. Gordon Meiklejohn (University of Colorado School of Medicine) and at Fort Dix by Dr. Harry M. Rose (Columbia University College of Physicians and Surgeons). The details of the results of these important investigations will be published shortly by the responsible investigators.

PROSPECTS FOR IMPROVEMENT OF VACCINES

Efforts to develop better vaccines have continued. Influenza virus vaccine has served as a useful model in these investigations. One objective is to purify virus suspensions and to isolate the essential antigens necessary for inducing protection by vaccination. The results of experiments carried out in the Virus Laboratory, Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, are promising. Dr. Hunein F. Maassab has found that high yields of influenza viruses can be obtained in large flasks containing infected chick kidney cell cultures. The virus suspensions harvested have far less nonviral material than do conventional suspensions grown in eggs. Drs. Fred M. Davenport and Albert V. Hennessy have developed a simplified method for purifying influenza virus suspensions, and for concentrating and purifying the protective antigens liberated by splitting the virus with ether. One would expect that a highly refined vaccine could be obtained by using these methods to treat virus grown in chick kidney culture. It is anticipated that such a refined vaccine will be better tolerated by the recipients.

Dr. Julius S. Youngner (University of Pittsburgh) has continued his studies on concentration, purification, and inactivation of many viruses by adsorption on the lipid hexadecylamine. This procedure offers promise for the development of more effective vaccines. Dr. Edwin D. Kilbourne (Cornell University Medical College) and Dr. Thomas P. Magill (Downstate Medical Center, Brooklyn, New York) have been attempting to develop mutant strains of influenza viruses that possess the properties one would desire for use in the manufacture of influenza vaccines. Results to date demonstrate that growth of virus in eggs can be greatly enhanced and the antigenic composition of strains modified by appropriate manipulations.

Comparative studies, carried out under Commission auspices in the early 1940's, on live influenza virus vaccines given to human volunteers, led to the conclusion that killed influenza virus vaccines were distinctly superior. Recent publications by Russian investigators on the efficacy of live attenuated influenza virus vaccines have stimulated interest in the properties of their vaccines. Through the good offices

of the National Institutes of Health, U.S. Public Health Service, 2 live Asian virus vaccines manufactured in Russia were made available to the Commission and were studied by Dr. Gordon Meiklejohn. He found that the vaccines were relatively easy to administer intranasally and were well tolerated by the recipients. Antibody response to vaccination, however, was disappointing. Persons devoid of Asian antibody before vaccination developed low levels after vaccination. Those with low or high levels before vaccination failed to exhibit a "booster" response. In parallel studies Dr. Meiklejohn demonstrated that inactivated influenza virus vaccines given subcutaneously produced higher and more uniform Asian antibody levels. Because attenuated live influenza virus vaccines are difficult to manufacture, produce immunity for only about 4 months, are unsuitable for children, and cannot be used in polyvalent mixtures at the current state of development, their use in the United States is not recommended.

RITUALISTIC SURGERY

The technical excellence of a surgeon's art is important, for it is this quality more than any other that makes his operations safe and effective. In the period of training it is an advantage for him to master the standard techniques so that they may become the scaffolding on which his surgical philosophy is built. Yet there are dangers in perfecting techniques: the dangers of becoming overly enamored of the craftsmanship involved and of being reluctant to adopt new methods. The surgeon knows that employment of new techniques may, until they are mastered, result in a temporary increase in postoperative complications. As a result of this knowledge his operations may become overstandardized. The decision as to what operation should be performed may be made on the basis of what operation the surgeon does most expertly instead of on what operation would be best for the patient. When this happens and when a technique has become standardized too rigidly the operation may become a mere corollary to the diagnosis. In such cases the reflex centers of the surgeon have taken control. It is the hand that guides the mind.—GEORGE CRILE, JR.: The Danger of Becoming Satisfied with Standardized Techniques (editorial). *Surgery, Gynecology & Obstetrics*, July 1960.

This Is Your A. M. A.

THE COMMUNICATIONS DIVISION, which is the public relations arm of the American Medical Association, had its beginning as part of the Council on Medical Service and Public Relations in 1943. Seven years later the Department of Public Relations was formed. In 1958 the department became the Communications Division—1 of 8 American Medical Association components reporting directly to the executive vice president.

Today, within the operating framework of the Communications Division are 8 separate departments—Media Relations, Special Services, Program Development, Services to Officers, American Medical Education Foundation, Medical Motion Pictures and Television, *Today's Health* magazine, and *The AMA News*.

The purpose of this article is to discuss the operations of the 2 periodicals—*Today's Health* and the *AMA News*—published by the Division for the Association. In subsequent articles, other activities of the Division will be explained.

Today's Health, the monthly magazine featuring articles of a general health nature for the lay public, was founded in 1923 under the name *Hygeia*. The new name was adopted in 1950. During the current year, *Today's Health* circulation reached an all-time high of 830,000 copies a month, placing it in the "major magazine" category of *Sports Illustrated*, *Esquire*, and *Living for Young Homemakers*.

Because of its appearance in the waiting rooms of some 140,000 member physicians, it has been estimated that authoritative health information is made available to nearly 40 million Americans each month via its pages.

Each issue carries at least 1 article on general medicine, child development, nutrition, travel and recreation, and safety and first aid. Other articles include such subjects as health-related community problems, health education material, and profiles of prominent men in medicine as well as of lay personalities with a health message for the public.

Numerous *Today's Health* articles have been reprinted recently in the *Congressional Record*, *Reader's Digest*, and the State Department's Russian-language magazine, *America Illustrated*. A number of new books have incorporated material from the magazine. Stories based on *Today's Health* articles and distributed via news releases are frequently quoted by newspapers and newscasters throughout the country.

The 88-page monthly is 8½ by 11 inches in size and is printed by the Baird-Ward Company in Nashville, Tenn. Wide use is made of 4-color covers and 4-color illustrations for editorial material.

The *AMA News*, the Association's newest publication, was published for the first time on 22 September 1958. Published biweekly, its purpose is to bring news of a socioeconomic nature to the nation's physicians.

Spontaneous acceptance of the newspaper required a press run increase of 41,327 in the first 2 months of publication. By mid-1960, circulation was 269,568, reaching more doctors than any other medical publication.

Although the *News* is still a relatively young publication, it has been widely quoted and reprinted both here and abroad in newspapers, magazines, state and

---

From the Council on National Security of the American Medical Association. The views and opinions expressed are not necessarily those of the Department of Defense.—EDITOR.

county medical journals, trade papers, hospital and health publications, chamber of commerce bulletins, pharmaceutical periodicals, college and university publications, insurance bulletins and magazines, farm journals, science and military publications, and reports of U.S. congressional committees.

News articles have served as the basis for editorials, quotes in editors' personal columns, comments in nationally syndicated health columns, network radio and television commentary, regular weekly health programs for radio stations, and weekly newspaper science and medicine departments.

Regular features include: capsules of the news, editorial viewpoint, quotes and comments, letters to the editor, on the legislative front, Washington briefs, scientific briefs, scanning the news, names in the news, medicolegal decisions, and diagnosing investments.

In addition to the news and editorial staff based in Chicago, a nation-wide corps of 60 "stringer" correspondents are constantly relaying news and feature material from their regional areas.

A readership survey made during recent months indicates that 89.6 percent of American physicians read the *News* regularly. More than 78 percent said they found it useful in their practice. When asked, "What do you like most about the *AMA News*?" the physicians mentioned breadth of coverage, timeliness, conciseness, and the fact that it covers news not covered by other medical publications.

The 16-page, 2-color *News* is printed by the Perry Printing Company, Inc., Waterloo, Wis., and is available on a complimentary basis to all physician members of the armed services. If you are not now receiving a copy of *The AMA News*, contact: Circulation and Records Department, American Medical Association, 535 North Dearborn, Chicago 10, Ill.

HOW TO AVOID MALPRACTICE SUITS

The material appearing in the medical journals not only keeps doctors up to date; it may also have the effect of increasing the doctor's medicolegal liability. A court may reason that if the dangers of a particular procedure have been reported in the medical literature, then the reputable physicians in the locality should know of such dangers and a physician who uses such a procedure must be guilty of malpractice . . . . Such articles not only increase the possibility of a lawsuit, they also make such suits harder to defend. Medical journals are a two-edged sword. They cannot cease publication merely because they are a possible benefit to dissatisfied patients, however. In the long run, the profession and the public are best served by honest and unbiased reporting in the medical press. The lesson of importance for all physicians, though, is *read your medical journals!*—GEORGE E. HALL: A Vicious Medicolegal Circle. *The New Physician*, November 1958.

New Books

Books received by the U.S. ARMED FORCES MEDICAL JOURNAL *are listed in this department for the information of readers, and as acknowledgment and appreciation of their receipt from the publishers.*

ADVANCES IN SPACE SCIENCE, edited by *Frederick I. Ordway, III*, with the assistance of an editorial advisory board. Vol 2. 450 pages; illustrated. Academic Press, New York, N.Y., 1960. Price $13.

RECENT ADVANCES IN CLINICAL PATHOLOGY, Series III, by various authors. General editor, *S. C. Dyke*, D.M. (Oxon.), F.R.C.P. (Lond.). Section editors: Bacteriology, *Mary Barber*, M.D. (Lond.), F.R.C.P. (Lond.); Chemical Pathology, *E. N. Allott*, D.M. (Oxon), F.R.C.P. (Lond.), F.R.I.C.; Hematology, *Rosemary Biggs*, M.D., M.Sc. (Lond.). Ph.D. (Toronto); Histology, *A. H. T. Robb-Smith*, M.D. (Lond.), F.R.C.P. (Lond.). 425 pages; illustrated. Little, Brown and Co., Boston, Mass., 1960. Price $11.50.

THE YEAR BOOK OF PATHOLOGY AND CLINICAL PATHOLOGY, (1959–1960 Year Book Series), edited by *William B. Wartman*, B.S., M.D. 455 pages; illustrated. Year Book Publishers, Inc., Chicago, Ill., 1960. Price $9.

NUTRITION AND PHYSICAL FITNESS, by *L. Jean Bogert*, Ph.D. 7th edition. 613 pages; illustrated. W. B. Saunders Co., Philadelphia, Pa., 1960. Price $6.

AN INTRODUCTION TO PHARMACOLOGY, by *J. J. Lewis*, with a foreword by *Stanley Alstead*, C.B.E., M.D., F.R.C.P.Ed., F.R.C.P. Lond., P.R.F.P.S. 726 pages; illustrated. Williams & Wilkins Co., Baltimore, Md., 1960. Price $11.

NONPENETRATING INJURIES OF THE ABDOMEN, by *Robert H. Kennedy*, B.A., M.D., F.A.C.S. 121 pages. Charles C Thomas, Publisher, Springfield, Ill., 1960. Price $4.75.

BIRD-HEADED DWARFS, Studies in Developmental Anthropology Including Human Proportions, by *Helmut P. G. Seckel*, M.D. 241 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1960. Price $10.

LEUKEMIA, Research and Clinical Practice, by *F. G. J. Hayhoe*, M.A., M.D. (Cantab.), M.R.C.P. (Lond). 335 pages; illustrated with 12 colored plates and 196 black-and-white illustrations. Little, Brown and Co., Boston, Mass., 1960. Price $16.

THE HEAD, NECK AND TRUNK, by *Daniel P. Quiring*, Ph.D. 2d edition, revised and edited by *John H. Warfel*, Ph.D. 124 pages; illustrated. Lea & Febiger, Philadelphia, Pa., 1960. Price $3.25.

PSYCHOTHERAPISTS IN ACTION, Explorations of the Therapist's Contribution to the Treatment Process, by *Hans H. Strupp*. 338 pages; illustrated. Grune & Stratton, Inc., New York, N.Y., 1960. Price $8.75.

RADIOLOGY AS A DIAGNOSTIC AID IN CLINICAL SURGERY, by *Howard Middlemiss*, M.D., F.F.R., D.M.R.D. 151 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1960. Price $7.50.

RECENT ADVANCES IN BIOLOGICAL PSYCHIATRY, Including a Havelock Ellis Centenary Symposium on Sexual Behavior, edited by *Joseph Wortis*, M.D. The proceedings of the 14th annual convention and scientific program of the Society of Biological Psychiatry, Atlantic City, June 1959. 417 pages; illustrated. Grune & Stratton, Inc., New York, N.Y., 1960. Price $13.50.

VIRAL INFECTIONS OF INFANCY AND CHILDHOOD, A Symposium of the Section on Microbiology, The New York Academy of Medicine, edited by *Harry M. Rose*, M.D. 244 pages; illustrated. Paul B. Hoeber, Inc., New York, N.Y., 1960. Price $8.

EPILEPSY and Related Disorders, by *William Gordon Lennox*, A.B., A.M., M.D., Sc.D. (Hon.), with the collaboration of *Margaret A. Lennox*, A.B., M.D. Vols. I and II. 1168 pages; illustrated. Little, Brown and Co., Boston, Mass., 1960. Price $13.50 for 2 vols.

LABORATORY MANUAL FOR GENERAL CHEMISTRY, by *Garth L. Lee*, Ph.D., and *Harris O. Van Orden*, Ph.D. 217 pages; illustrated. W. B. Saunders Co., Philadelphia, Pa., 1960. Price $3.75.

MANUAL OF HAND INJURIES, by *H. Minor Nichols*, M.D., with a foreword by *Michael L. Mason*, M.D., 2d edition. 400 pages; illustrated. Year Book Publishers, Inc., Chicago, Ill., 1960. Price $11.

PROCEEDINGS OF A SYMPOSIUM ON IMMUNIZATION IN CHILDHOOD, held in the Wellcome Building, London, 4th to 6th May 1959. 139 pages; illustrated. Williams & Wilkins Co., Baltimore, Md., 1960. Price $4.25.

CHILD DEVELOPMENT, Physical and Psychologic Growth Through Adolescence, by *Marion E. Breckenridge*, M.S., and *E. Lee Vincent*, Ph.D. 4th ed. 648 pages; illustrated. W. B. Saunders Co., Philadelphia, Pa., 1960. Price $6.50.

ATTENUATED INFECTION, The Germ Theory in Contemporary Perspective, by *Harold J. Simon*, M.D., Ph.D., forewords by *Rene J. Dubos*, Ph.D., and *Walsh McDermott*, M.D. 349 pages; illustrated. J. B. Lippincott Co., Philadelphia, Pa., 1960. Price $10.

INDUSTRIAL PULMONARY DISEASES, A Symposium held at the Postgraduate Medical School of London, 18th–20th September 1957, and 25th–27th March 1958, edited by *E. J. King*, M.A., D.Sc., F.R.I.C., and *C. M. Fletcher*, C.B.E., M.D. (Cantab.), F.R.C.P. 273 pages; illustrated. Little, Brown and Co., Boston, Mass., 1960. Price $8.50.

A HISTORY OF PSYCHIATRY, by *Jerome M. Schneck*, A.B., M.D. 196 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1960. Price $5.50.

DENTAL CLINICS OF NORTH AMERICA, July 1960, Symposia on I. Minimizing Prosthodontic Failures, consulting editor, *S. Howard Payne*, D.D.S., and II. Dentistry for the Handicapped, consulting editor, *Manual M. Album*, D.D.S. 523 pages; illustrated. W. B. Saunders Co., Philadelphia, Pa., 1960. Price $4.

INTRA-OSSEOUS VENOGRAPHY, by *Robert A. Schobinger*, M.D., with a foreword by *Philip J. Hodes*, M.D. 243 pages; illustrated. Grune & Stratton, Inc., New York, N.Y., 1960. Price $14.50.

INTERNAL MEDICINE, A Physiologic and Clinical Approach to Disease, by *Robert P. McCombs*, B.S., M.D., F.A.C.P. 2d ed. 750 pages; illustrated. Year Book Publishers Inc., Chicago, Ill., 1960. Price $10.50.

THE HEART IN INDUSTRY, by twenty-four authors, edited by *Leon J. Warshaw*, M.D., F.A.C.P., with a foreword by *Irving S. Wright*, M.D. 677 pages. Paul B. Hoeber, Inc., Medical Division of Harper & Bros., New York, N.Y., 1960. Price $16.

CLINICAL ORTHOPAEDICS, Number 16, edited by *Anthony F. DePalma*, with the assistance of the Associate Editors, the Board of Advisory Editors and the Board of Corresponding Editors. 315 pages; illustrated. J. B. Lippincott Co., Philadelphia, Pa., 1960. Price $7.50.

NEOPLASMS OF BONE AND RELATED CONDITIONS, by *Bradley L. Coley, M.D.* 2d ed. 863 pages; illustrated. Paul B. Hoeber, Inc., Medical Division of Harper & Bros., New York, N.Y., 1960. Price $30.

THE USE OF LSD IN PSYCHOTHERAPY, Transactions of a Conference on D-Lysergic Acid Diethylamide (LSD–25) April 22, 23, and 24, 1959, Princeton, N.J., edited by *Harold A. Abramson*, M.D. Sponsored by the Josiah Macy, Jr. Foundation, New York, N.Y. 304 pages; illustrated. Madison Printing Co., Inc., Madison, N.J., 1960. Price $5.

TEACHING FUNDAMENTALS OF NURSING, Method, Content and Evaluation, by *Elinor V. Fuerst*, R.N., M.A., and *LuVerne Wolff*, R.N., M.A. 3d ed. 111 pages. J. B. Lippincott Co., Philadelphia, Pa., 1960. Price $2.50.

BIOMECHANICS OF THE CENTRAL NERVOUS SYSTEM, Some Basic Normal and Pathologic Phenomena, by *Alf Breig*. 183 pages; illustrated. Year Book Publisher, Inc., Chicago, Ill., 1960. Price $8.50.

A SHORT HISTORY OF OBSTETRICS AND GYNECOLOGY, by *Theodore Cianfrani*, M.D. 449 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1960. Price $12.50.

RADIATION, Use and Control in Industrial Application, by *Charles Wesley Shilling*, M.D., Sc.D. 223 pages; illustrated. Grune & Stratton, Inc., New York, N.Y., 1960. Price $6.75.

MANUAL FOR EXAMINATION OF PATIENTS. School of Medicine and North Carolina Memorial Hospital, The University of North Carolina, Chapel Hill, N.C. 231 pages. Year Book Publishers, Inc., Chicago, Ill., 1960. Price $4.50.

DECISION MAKING IN HOSPITAL ADMINISTRATION AND MEDICAL CARE, A Casebook, by *James A. Hamilton*, 710 pages. University of Minnesota Press, Minneapolis, Minn., 1960. Price $10.50.

FLUID BALANCE IN OBSTETRICS, A Critical Review, by *Philip Rhodes*, M.A., M.B., F.R.C.S. (Eng.), M.R.C.O.G. 109 pages. Year Book Publishers, Inc., Chicago, Ill., 1960. Price $5.75.

GLOSSARY OF WORDS AND PHRASES USED IN RADIOLOGY AND NUCLEAR MEDICINE, Prepared from Various Sources for Medical Secretaries, X-ray Technicians, Medical Students and Residents in Radiology, by *Lewis E. Etter*, B.S., M.D., F.A.C.R., with a section of Suggested Terminology for Roentgenological Reports, devised by Doctors *Fisher*, *Bovard* and *Bason* for the Pennsylvania Radiological Society. Foreword by *Olive G. Johnson*, A.B. 203 pages. Charles C Thomas, Publisher, Springfield, Ill., 1960. Price $8.50.

THE YEAR BOOK OF ENDOCRINOLOGY (1959–1960 Year Book Series), edited by *Gilbert S. Gordan*, M.D., Ph.D., F.A.C.P. 384 pages; illustrated. Year Book Publishers, Inc., Chicago, Ill., 1960. Price $8.

GASTRIC CYTOLOGY, Principles, Methods and Results, by *Rudolf Otto Karl Schade*, M.D. (Dunelm), M.D. (Tubingen), L.R.C.P., M.R.C.S. 83 pages; illustrated. Williams & Wilkins Co., Baltimore, Md., 1960. Price $8.

NEUROPHARMACOLOGY, Transactions of the Fifth Conference May 27, 28, and 29, 1959, Princeton, N.J., edited by *Harold A. Abramson*, M.D. 251 pages; illustrated. Sponsored by the Josiah Macy, Jr. Foundation, New York, N.Y., 1960. Madison Printing Co., Madison, N.J. Price $6.

ORAL PATHOLOGY, by *Kurt H. Thoma*, D.M.D., Dr. med. dent. h.c. (Zurich); F.D.S.R.C.S. (Eng.); Hon. F.D.S.R.C.S. (Edin.); F.A.C.D., and *Henry M. Goldman*, D.M.D., F.A.C.D. 5th ed. 1523 pages; illustrated. C. V. Mosby Co., St. Louis, Mo., 1960. Price $27.50.

NOYES' ORAL HISTOLOGY AND EMBRYOLOGY, with Laboratory Directions. 8th ed., revised and edited by *Isaac Schour*, B.S., D.D.S., M.S., Ph.D., Sc.D. 440 pages; illustrated. Lea & Febiger, Philadelphia, Pa., 1960. Price $11.50.

THE CLINICAL USE OF ALDOSTERONE ANTAGONISTS, compiled and edited by *Frederic C. Bartter*, with 23 contributors. 211 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1960. Price $5.

THE NATURE OF HUMAN CONFLICTS, or Emotion, Conflict and Will, An Objective Study of Disorganization and Control of Human Behavior, by *A. R. Luria*. Translated from the Russian and edited by *W. Horsley Gantt*, with a foreword by *Adolf Meyer*. 431 pages; illustrated. Grove Press, Inc., New York, N.Y., 1960. Price $2.45.

MANUAL OF BLOOD MORPHOLOGY, by *Lydia Schudel*. 9th ed., revised. 53 pages; with 18 colored tables. J. B. Lippincott Co., Philadelphia, Pa., 1960. Price $4.50.

SIMPLIFIED NURSING, The Essentials of Practical Nursing, by *Ella M. Thompson*, B.S., R.N., and *Margaret LeBaron*, R.N. 7th ed. 938 pages; illustrated. J. B. Lippincott Co., Philadelphia, Pa., 1960. Price $5.50.

DISEASES OF THE NEWBORN, by *Alexander J. Schaffer*, M.D., with a section on Neonatal Cardiology, by *Milton Markowitz*, M.D. 878 pages; illustrated. W. B. Saunders Co., Philadelphia, Pa., 1960. Price $20.

CLINICAL TROPICAL DISEASES, by *A. R. D. Adams* and *B. G. Maegraith*. 2d ed. 540 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1960. Price $11.50.

NEUROLOGY SIMPLIFIED, A Practical Approach to the Early Diagnosis and Treatment of Neurologic Diseases written especially for General Practitioners and Students, by *David Joseph LaFia*, M.D., with a foreword by *A. Earl Walker*, M.D. 175 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1960. Price $6.75.

THE TRANSPARENCY OF THE CORNEA, A Symposium organized by the Council for International Organizations of Medical Sciences, established under the joint auspices of UNESCO and WHO, edited by Sir *Stewart Duke-Elder*, and *E. S. Perkins*. 268 pages; illustrated, Charles C Thomas, Publisher, Springfield, Ill., 1960. Price $10.

ELECTROENCEPHALOGRAPHY IN ANESTHESIOLOGY, by *Albert Faulconer, Jr.*, M.D., M.S., and *Reginald G. Bickford*, M.B., Ch.B., M.R.C.P. 90 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1960. Price $4.75.

MEDICAL PHYSIOLOGY AND BIOPHYSICS, edited by *Theodore C. Ruch*, Ph.D., and *John Fulton*, M.D. 18th edition of Howell's Textbook of Physiology. 1232 pages; illustrated. W. B. Saunders Co., Philadelphia, Pa., 1960. Price $16.

LECTURE NOTES ON OPHTHALMOLOGY, by *Patrick D. Trevor-Roper*, M.A., M.D., B. Chir, (Cantab.), F.R.C.S., D.O.M.S. (Eng.). 94 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1960. Price $3.50.

INTRASPINAL TUMORS OF CHILDHOOD, by *Robert W. Rand*, M.D., Ph.D., and *Carl W. Rand*, M.D., 560 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1960. Price $16.50.

EXPERIENCES WITH CONGENITAL BILIARY ATRESIA, by *Julian A. Sterling*, M.D., Sc.D., F.A.C.S. 68 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1960. Price $5.50.

DISEASES OF THE NAILS, by *V. Pardo-Castello*, M.D., and *Osvaldo A. Pardo*, M.D., with a foreword by the late *Howard Fox*, M.D. 3d ed. 284 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1960. Price $8.50.

U.S. GOVERNMENT PRINTING OFFICE: 1960 O—562174